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The Menopause—An Introduction

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THE MENOPAUSE is an integral part of the process of aging in women. It is not a new experience in the life of women, but has perhaps been more widely publicized and discussed in the last decade because of means for endocrine therapy.

Historically, the use of the word menopause appears to be of relatively recent origin. The Oxford English Dictionary quotes J. M. Good who stated in 1834 that "when menstruation is about to cease, the period is called the 'change of turn of life,' " and cites Peaslee who in 1872 referred to "the 30 or 35 years of menstrual life, i.e. from puberty to the menopause."

An instructive treatise, "The Change of Life," by Edward John Tilt (1) has a well-informed chapter on the physiology of the "change of life," with statistical data which are useful today. This work was written before the clinical use of hormones and the author ascribes the multiform disturbances of the menopause to disease of the "ganglionic nervous system." The frequent reference to the psychosomatic manifestations of the menopause in the several chapters of this symposium indicate that Tilt was a very careful observer and physician for his time.

The cessation of menstruation and the decline and termination of the reproductive capacity of women is an aspect of aging, as the menarche is the keystone of development and maturation. During puberty menstruation is usually irregular, with occasional episodes of menorrhagia. This implies that the factors which regulate menstrual and ovulation rhythm do not all mature or become effective at the same time. The gradual loss of menstrual and ovulatory rhythm in the premenopausal woman indicates that the rate of involution or aging of the endocrine organs and the genital tract may vary as did their maturation during puberty.

The woman of menopausal years has experienced not only the involution of the reproductive organs, with accompanying endocrine disturbances, but also many other changes, physical and psychological, which accompany the process of aging in either sex.

From the standpoint of National health the medical problems of the older woman become increasingly important. The augmented average age of the population and the greater number of both men and women in the older age groups have focused attention on medical problems most frequently seen in the these groups. The report of the United States census

of 1940 shows that there were in that year 16,036,947 white women aged 45 or over. This group will increase in numbers for several decades. The need for careful appraisal of physiological and psychological disturbances in women of menopausal and post-menopausal age is apparent.

Many studies in the physiology of human reproduction have been made possible because of extensive experimental work on lower animals. Our information on the cessation of reproductive life in woman is, however, much more extensive than that on any of the lower animals.

The general practice in breeding either with laboratory or domestic animals is to retire animals from active service some time after the animal has reached middle age. The actual efficiency of reproductive performance has declined to such a degree that it is not economically profitable to continue the older animals for breeding purposes. Among the meat-producing domestic animals there are definite advantages in disposing of breeding stock before old age appears.

Under modern conditions of care and nutrition, it is probable that many pure line pedigreed horses are kept to near the maximum of their life span. No information is available on the reproductive performance or life span of pedigreed dogs. These animals should afford substantial data, since they receive excellent care and are usually kept until death ensues.

A study of the fertility of Morgan mares under controlled conditions over a ten-year period has been made by Lambert, Speelman and Phillips (2). The maximum longevity of horses is not known, but it may be accepted that a horse is old at 25 years. In this series of mares, the highest fertility was between 7 and 14 years. A decrease occurred after 15 years and marked decrease in fertility occurred after 19. Among thoroughbreds, where blood lines are economically important, mares may give birth to colts when at an advanced age. As an instance, "Yankee Maid" gave birth to a live colt when 24 years of age. Similarly, there is record of two Clydesdale mares, each of which bore colts when 20 and 21 years of age and later died at age 25 (report from *Scottish Farmer*).

Sheep also cease to be economically productive breeders after the sixth year, according to Terrill and Stoehr (3). In their herd of 8,000 sheep there were 87 eight-year-old ewes and 18 nine-year-olds which lambed. Isolated instances of goats and cows which have produced young between the 25th and 29th year have been reported. Thus, while the decline of fertility is marked after middle life, domestic animals do produce young at ages near the upper limit of the life span.

Actual total breeding performance of the laboratory rat has not been recorded. The extensive studies in the rat by Slonaker (4) indicate that this animal passes through characteristic estrus cycles, as measured by cycles of voluntary activity, over most of their life span. The average age of cessation of cycles was 755 days. The average total life span of the female rats of this colony is not given, but it appears to be approximately 900 days.

It is difficult to make any comparison between the end of reproductive life in animals and that of woman. Data from the Bureau of Census lists recorded births by age of mother (1940, Table 47, p. 672). The recorded age is subject to possible error of fact or memory by the registrant. The data show that the births for the age group 45–49 were 1.2 per 1000 for white women and 1.3 per thousand for all races. For the age group 50–54 there were no births among white women and 1 per 10,000 for all races. This may indicate either that pregnancy avoidance is more efficient in the older age groups of white women, or that white women have passed the reproductive period earlier than the other races, or that the stated age among the non-white woman is subject to some error.

The older literature, as summarized by Tilt (1882), lists 167 women 50 years of age or older who bore children in England between 1831 and 1835. A woman may give birth to a living child after the age of 50, but this is rare.

Detailed studies of the ovaries of aging woman and lower animals have not yet been made. At the menopause, most, if not all, of the ova and follicles have disappeared from the ovaries of woman, although apparently normal corpora lutea in women over 50 have been reported.

It is not known if menstruation in the monkey ceases before old age is reached. In two aged Rhesus monkeys numerous ova and growing and atretic follicles have been observed (Engle, *et al.*, 5).

Among domestic animals, the ovary of old cows has been described by Petskoi (6) who states that a marked decrease in the number of ova occurred after 14–15 years of age. No germinal epithelium was found in cows older than 16 years. A general destruction of follicles occurred in old age, the majority of them being cystic.

The ovaries of rats of 1000 days have many ova and frequently many follicles in atresia, even though the animals have passed reproductive capacity (Engle 7).

It is possible that the presence of ovarian ova and some follicular growth and hormone production constitute an important difference in the aging process between woman and other mammals, which accounts for the fact that the reproductive capacity may extend over a larger proportion of the life span in the lower animals than in woman.

From the few studies cited and from the practical experience of animal breeders it is seen that all known mammals, like women, are most fertile before middle life and show a declining fertility as old age approaches. Unlike women, however, some animals may reproduce during the years of actual old age.

There is no evidence of any endocrine disturbance in the aging females of lower animals which gives rise to any symptoms characteristic of the menopause in women. Many animals have an increased amount of gonadotropic hormone stored in the hypophysis and appearing in the circulating blood after castration but in no animal, including the monkey, is there increased urinary excretion of gonadotropin comparable to that of the menopausal woman.

The large component of psychosomatic manifestations associated with cessation of the menses and involution of the genital organs definitely limits the syndrome of this period of life to the human.

The Medical Women's Federation (England, 8) issued a report on the menopause based on data obtained by interview with 1179 women who had experienced no menstruation for at least five years. Of this group, 15.8% had passed through this period with no symptoms, while 10.3% reported that they were incapacitated for this period. Among this latter group was one woman who had always been incapacitated by a weak heart but was 90 years old at interview. Of classified complaints, flushing was most frequent (62.3%), while headaches (44.6%) and nervous instability (30.9%) were also frequent.

An analysis of any group of subjective symptoms presents a problem to the clinician. Thirty per cent of the above group reported nervous instability as a menopausal symptom. It is probable that some degree of psychoneurotic behavior may have existed in these women long before the cessation of the menses, behavior that is not directly related to the menopause. These symptoms represent disturbances more extensive than can be accounted for by a decreased estrogen level or heightened gonadotropic hormone titer.

The degree to which the more nebulous psychosomatic manifestations of the aging process in women or in men may be related to altered hormone balance must be left to future investigation. The physician must know that the disturbances at the "change of life" or menopause are more than an endocrine imbalance. If the symptoms are solely due to estrogen deprivation, then adequate replacement therapy will suffice. If the symptoms are a result of inevitable and irrevocable changes arising from the process of aging, then wise counsel will aid in personal and mental adjustments to the condition.

In almost every case the physician who gives advice or recommends therapy to a woman of menopausal years must deal first and primarily with a disturbed patient and only secondarily with an individual having lowered estrogen reserves.

The purpose of this symposium is to present for the guidance of the physician an appraisal of the woman of menopause years with suggestions for such therapy as may be needed.

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The Menopausal Patient

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THE TERM menopause, strictly interpreted, means the cessation of menstruation. As used clinically it is made to include many phenomena commonly seen in women around the menopausal age. That age varies greatly in different women. In a few, menstruation stops before forty; in a few it may continue until well on to fifty-five. The average age is between forty-six and forty-eight.

In a small minority of women the stoppage is abrupt. They menstruate regularly and normally up to a certain month and thereafter have no further uterine bleeding of any kind. In the great majority the menstrual periods gradually diminish in amount (in a few there may be an increased flow), they skip a month, then have a period, may be regular for a month or two, then skip one or two or three months, bleed again, and so on until there is a final cessation. During all this time they may be having so-called menopausal symptoms. Some women have these symptoms even when still menstruating regularly.

These phenomena are due to the gradual diminution in estrogen production as the result of the aging of the ovaries. During this time ovulation may or may not be occurring. Many of the irregular "periods" are not true menstruation but simply anovulatory bleeding. That ovulation may occur until quite a late age is proved by the occasional case of a woman of forty-eight or more who, ceasing to menstruate and believing the menopause established, finds herself pregnant.

In the vast majority of women the menopause occurs without any marked physical or emotional upset. The clinician sees only those in whom symptoms are severe or those who, from the reading of lay literature or from listening to the conversation of their companions round the tea or bridge table, get an exaggerated picture of the ills and troubles that may befall them at this time.

Let us look at this second class first. What they need most is a short talk from their doctor explaining just what the menopause is and what it means to them. It should be explained as a natural phenomenon, any small disturbance, such as hot flushes, sudden perspirations, occasional dizziness, being due to disturbed vasomotor control which will become readjusted in time. Many of them fear that with the advent of the menopause they will become less attractive to their husbands and that their sex life will cease. On this they can be reassured. Sexual desire is preserved in most women for many years after menstruation ceases. Others fear that there may be mental deterioration or even the risk of mental derangement at this time. It should be explained to them that there is no such risk in the hitherto stable.

Many of these women believe that the supposedly evil day can be postponed by the taking of hormones, for they are constantly learning about hormones from their friends. They ask that such medicaments be prescribed or confess that they have begun taking them without prescription.

Such cases, whether presenting minor symptoms or none at all, should be taken seriously and a complete physical and laboratory investigation made; otherwise they will drift to someone who will prescribe for them out of hand and so will start them on their "hormonal" career. If this examination reveals normal findings, as it usually does, a further talk should be given in a little more detail. It can be explained to them in simple language that the hormones of which they speak are estrogens

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and that the taking of these is not going to help keep the ovarian function going; that, on the contrary, they are likely to depress it by depressing the pituitary; that the treatment is a substitution therapy more likely to make the ovary "lazy" and "lie down on its job," rather than to stimulate it and make it last longer; that once begun the dosage may have to be increased and continued for an indefinite time.

With some patients talking and explanation are not enough; they require something more tangible. For such, a prescription for iron in some form, if they are anemic, a bitter tonic, such as nux vomica, aromatic spirit of ammonia mixture, or a mild sedative, such as one-quarter or one-half grain of luminal two or three times daily, may be in order.

Now we come to the patients who have definite and pronounced symptoms. By far the commonest of these is the hot flush—a sudden feeling of heat in the head, neck and chest, often accompanied by diffuse or patchy flushing of the skin and a sudden, profuse perspiration. In some there is only the feeling of heat, with no flushing and no perspiration. These episodes are sometimes referred to as "hot flashes." In some there are sudden attacks of perspiration without much feeling of heat. These flushes and flashes may begin in the feet or in the lower back and then spread rapidly over the rest of the body. The perspiration is often very profuse and may be followed by a more prolonged period of severe chill. The whole episode is accompanied by a feeling of extreme nervousness and self-consciousness and mild mental perturbation. The attacks occur at varying intervals during the day. Their unpredictability makes the patient fear to meet people, go to business, or take part in social functions. When they occur at night, profuse perspiration may necessitate several changes of night garments and even bed clothes. It is little wonder that with the frequent repetition of these attacks the patient becomes generally nervous and apprehensive, believes her memory to be failing, has difficulty in concentrating, lacks energy, tires easily, and is generally miserable and depressed.

The above is the picture of an extreme case, fortunately not very common. From it there are all gradations down to the woman who has no symptoms at all. The average woman experiences these flushes and flashes in minor degree over a period of a few months, a year, or longer. Symptoms are apt to be worse in those without definite work or responsibility. The business woman or the active housewife is less likely to suffer as much as one of the "idle rich."

These vasomotor disturbances are certainly due to hormonal imbalance. Others will discuss the question as to whether the effects are due to diminished estrogenic hormone or to increased gonadotropic hormone in the circulation. The fact that in the great majority of cases quick relief is given by the administration of estrogens does not settle the question, for this may act either as a substitution therapy or as a depressant of pituitary function and so to a diminution of circulating gonadotropins. Possibly the effects are the result of both.

In severe cases the quickest relief is given by the administration of an estrogen by intramuscular injection, beginning with 10,000 international units twice or thrice weekly. Some patients may require even larger initial doses. It should be explained to the patient at the outset that the object to be kept constantly in mind is to use the minimum dosage at the longest possible intervals compatible with the control of symptoms and that, when symptoms are controlled, the dosage should be gradually diminished and the intervals increased. When dosage is diminished, minor recurrence of symptoms should not necessarily call for an increase of dosage. It is better for her to bear these lesser ills for a time and be "weaned" completely from the drug rather than continue with it over a period of years as happens in many cases. Estrogens are habit-forming drugs and patients should be warned accordingly. In most cases, when the severe symptoms are under control by intramuscular medication, the patient can be kept comfortable and happy with one of the oral preparations. With these, as with the others, the aim should always be a gradual diminution of the dosage.

When the patient's chief complaints are lack of energy, lassitude, easy fatigability, increase in weight, or sleeplessness, a basal-metabolic-rate determination is in order. Indeed this

should be done in all cases. It is our experience that with minus readings, which under other circumstances would be considered as within normal limits, thyroid therapy gives excellent results in alleviating some or all of the foregoing symptoms. As a rule the therapy need not be continued for long periods of time. It is certainly worth trying before starting the patient on either estrogens or androgens.

The irregularity of the periods in women at the menopausal age often poses a problem to the clinician. Irregular bleeding always suggests to him the possibility of carcinoma in cervix or corpus. The former can be excluded by palpation, inspection, and biopsy of the cervix and cervical canal. The latter can be excluded only by a systematic curettage of the endometrium. When ought the latter to be urged? A good general rule to go by is to urge it if there is irregular "spotting" or if what looks like a "period" is followed by intermittent bleeding, no matter how slight. Many women after several months of amenorrhea have what they describe as a normal period. It begins in the same way as they are accustomed to, the flow is of the usual character, and it lasts the average length of time; it stops completely at the end of a certain number of days and there is no blood-stained discharge following it. With such a history, curettage can be safely postponed but should be insisted upon if there is recurrence of bleeding, no matter how slight, at any subsequent date.

With so many women taking estrogens for the control of post-menopausal symptoms, gynecologists are seeing more and more cases of recurrence of vaginal bleeding, sometimes years after the last menstrual period. Here again, if the bleeding has lasted for only a few days and has stopped completely, a diagnostic curettage can be postponed, provided ordinary physical examination shows the pelvic organs to be normal. Estrogenic hormone administration should be stopped completely. If no further bleeding occurs it may be concluded that the former bleeding came from a proliferative endometrium resulting from the estrogen administered. Any further bleeding—after medication has been stopped—should call for a diagnostic curettage. Should androgen therapy prove successful in controlling menopausal symptoms this bugbear of recurring bleeding would be removed. It may also come to be the best therapy in those women who suffer from severe hot flushes and flashes while still menstruating regularly, for in such the estrogens often cause a great increase in the blood loss.

Following the menopause, there is a gradual atrophy of all the pelvic organs. The labia get smaller, the vagina contracts, the vaginal fornices become shallower, the cervix shrinks, the uterus diminishes in size and the pelvic floor muscles and fascia get less heavy. If anatomical conditions have been normal prior to this, the patient experiences no disability. If, however, there has been damage done to pelvic floor supports, in previous childbirth, such conditions as cystocele, rectocele and prolapse of the uterus may manifest themselves for the first time after the menopause. Likewise, most cases of uterine prolapse and of cystocele in nulliparous women develop in the post-menopausal years. When such conditions exist prior to the menopause they are likely to become aggravated after it and to go on getting progressively worse.

Kraurosis vulvae, an atrophic condition of the mucous membrane round the vaginal orifice and in the vestibule and urethra, is likewise a post-menopausal condition. Most cases of marked leucoplakia of the vulva are also seen in women who have ceased to menstruate. Both may be benefited by the administration of estrogens or their application locally. When, however, leucoplakia has gone to the stage of irritation and fissuring local excision gives the only permanent relief.

Arthritis with definite structural changes in the joint tissues and joint pains without physical signs not infrequently begin at the menopausal age. Just how much the hormonal imbalance is responsible is not clear. Some, but by no means the majority of such patients, seem to be benefited by estrogen therapy.

The interest in health and disease and the diffusion of knowledge of things medical among the laity is a feature of modern life. Unfortunately much that is presented in the lay press and read with avidity by the lay public is written with the object of arresting attention rather than of imparting accurate knowledge. It is the function of the physician

to correct, with his individual patient, the distorted ideas she may have acquired. In no field is this more important than that covering the menopause.

SUMMARY

The menopausal patient is pictured as she presents herself to the clinician. The importance of explaining to these patients what the menopause is is emphasized. Hormonal therapy should be withheld unless the symptoms are severe. When given, hormones should be prescribed in the smallest effective dosage and gradually withdrawn. The problem of irregular uterine bleeding at and after the menopause is discussed in relation to the possibility of its being due to carcinoma of cervix or endometrium. The effect of ovarian atrophy on the other pelvic organs is mentioned.

Menopausal and Post-Menopausal Anatomic Changes in Uterus and Vagina

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UNTIL recent years the simple concept which prevailed as to the hormonology of the menopause was that at this phase the ovaries cease to function, bringing about retrogressive and atrophic changes in the tubes, uterus and vagina. As regards the inauguration of the menstrual function at puberty, the general view was equally simple, namely that the awakening of estrogenic activity of the ovaries brings about hypertrophic and developmental changes throughout the genital tract. While there is no doubt as to the development or retrogression which in general parallels ovarian activity or inactivity, respectively, we have come to realize that neither the puberal nor the menopausal epoch is an abrupt one and that there are many individual variations and gradations in the hormonal and histologic phenomena encountered at the two extremes of menstrual life.

To appreciate fully the phenomena of the menopause, it is well to contrast them with those which occur at the opposite end of menstrual life, namely puberty, when cyclic ovarian function is inaugurated. Long before the actual beginning of menstrual function at puberty, estrogen is produced by the ovary from follicles which advance to various degrees of maturity. While there appear to have been no direct observations on the point, it is probable that this increasing prepuberal activity of the ovary would be reflected in some degree of proliferative activity of the endometrium. When the wave-like estrogenic influence of the ovary reaches a sufficiently high level, periodic bleeding phases are induced, corresponding to the anovulatory cycles which characterize the early menstrual life of a considerable proportion of puberal girls.

No one can speak with any authority as to the numerical incidence of this type of cycle as compared with ovulatory cycles, for the simple reason that there has been no systematic study of the endometrium in a sufficiently large number of girls of this age period who are menstruating with ostensible normality. That this sequence of events is common in early menstrual life is indicated by the frequency with which it is encountered in the numerous instances of functional menorrhagia at this age and there is no reasonable doubt that this pathologic disorder represents only an exaggeration, often of mild degree, of the anovulatory cycles exhibited by many girls in whom the menstrual amount and rhythm are within normal bounds. This statement would seem to be supported by the few scattered endometrial studies made on young girls in whom menstruation is clinically normal (1). On the other hand, there is equally little doubt that in a large proportion of girls, possibly because of brisker estrogenic output and thereby earlier activation of the luteinizing gonadatrophic factor of the pituitary, ovulation occurs with the first cycle and recurs regularly thereafter. As already mentioned, it seems futile to discuss the relative numerical incidence of these variations but it is worth while emphasizing their existence, as a background for the discussion of our immediate subject.

The normal variations in the hormonal relations and histology observed at and after the time of the menopause appear to be quite similar to those at and before the menarche, but in reverse. These variations concern even the clinical aspects of menstruation. Just as the beginning of menstruation may be marked by the rather abrupt institution of normal menstruation and normal menstrual tempo, so may the function cease very abruptly. More fre-

quently, however, its disappearance is more gradual, with the occurrence of increasing periods of amenorrhea, corresponding to the "dodging period" exhibited by so many girls in the puberal and early adolescent years. While women are warned, as a part of the cancer-prevention program, that all menstrual excess is abnormal, the fact remains that there is much individual variability in the amount of menstrual flow during the phase of premenopausal irregularity. The excess may be so extreme as to be clearly pathological, and functional bleeding of this type is, as a matter of fact, far more common than it is at puberty or in early adolescence. While the ideal menopause is one in which the amount as well as the frequency of the menstrual periods gradually taper off, the fact remains that minor degrees of menstrual excess are relatively common.

These clinical facts are mentioned because of their obvious relation to the histology of the uterus, especially the endometrium, at this epoch. The study in many laboratories of innumerable uteri before and after the menopause has established the essential role played by the ovarian estrogen in the growth and development of the uterus. This applies to the myometrium as well as the endometrium, and the decreased size of the postmenopausal organ is obviously due to the withdrawal of the specific growth-promoting influence of estrogen.

It is in the endometrium that one sees the individual histological variations which in large measure reflect the variations in the hormonal sequence of events which may occur at this time. If one studies uteri well before and long after the menopause, there will be no doubt of the generally retrogressive nature of the menopausal transition. But there are all sorts of histological variations in individual women during the immediately transitional years. On the basis of histology alone, one would find it difficult to believe that there is not much flexibility to the old doctrine of Zondek (2) that the characteristic menopausal sequence of events is, first, a phase of "hyperfolliculinism," then one of "hypofolliculinism" and finally one of "polyprolanism," to use the terms originally employed by Zondek.

To revert again to the useful comparison with puberty, the cycles may be of ovulatory character to the very end of menstrual life. On the other hand, ovulation may be inconstant or it may be totally absent for considerable periods of time before the actual cessation of the menstrual function. On this point we have a large body of evidence as a result of the endometrial studies now so readily available by biopsy. Unfortunately, most of these studies have been made on a selected group, those with sterility as a clinical indication for study. The figures reported by various authors as to the incidence of the anovulatory type of cycles in such patients show wide variation (3–5) and they cannot, of course, be taken as an index of the numerical incidence of the anovulatory cycle in normal, regularly menstruating women. In a series of 31 such normal women, Morton and Hayden (6) observed only 7 anovulatory cycles in 142 menstrual periods which were studied. Levan and Szants (7), in a very recent paper, report an incidence of 5.36 per cent of anovulatory cycles in a similar group of women. Like most authors they find the incidence greater in women approaching the middle period of life. In the monkey, the relative frequency of anovulatory cycles has long been known from the studies of Corner (8), Hartman (9) and others.

Other evidence as to the comparative frequency of anovulatory cycles, especially toward middle life, is furnished by the great frequency, especially at that epoch of life, of functional bleeding, most frequently of the type which represents an aberration or exaggeration of the anovulatory cycle (10).

The line between anovulatory cycles with little or no menstrual excess and those with pathological menorrhagia is a rather shadowy one and from the standpoint of endometrial histology, the picture may be identical. This is not, of course, to say that all cases of functional bleeding are to be placed in this anovulatory category, for it has been established that such bleeding may occur from any type of endometrium, whether hyperplastic, atrophic or actively secretory. There is no need for elaborating this point here, for it would involve speculative discussion of such poorly understood problems as individual variations in endometrial responsiveness or refractori-

ness, differentiation between growth and bleeding thresholds of the endometrium, and the behavior of the endometrial vascular apparatus. On this latter point, an obviously important one, gynecologists have thus far contributed very little and we must still utilize the results of the important animal experimental studies of Markee (11), Daron (12), and Okkels and Engle (13) as a basis for our concepts as to the behavior of the endometrial blood vessels. It is obvious that direct studies of this point in the human offer a field rich in potentiality.

While anovulatory cycles may occur at any age, it seems certain that they are far more common in the premenopausal years than they are in younger women. This would be circumstantially suggested by the great frequency of the anovulatory type of cycle in functional bleeding at this phase and, even more, by its relatively high incidence in cases of sterility of women beyond 35 and even more after 40. It is obvious that ovulation tests by the common method of endometrial biopsy cannot be made month after month in any large group of women, so that our ideas as to the relative infertility of women imposed by the relatively and probably increasingly frequent occurrence of anovulatory cycles must necessarily be in the nature of general impressions, which cannot yet be statistically supported.

It must again be emphasized, however, that ovulatory cycles may and do persist until the very end of menstrual life in a very large proportion—perhaps the great majority—of women. Again, characteristically, ovulatory cycles may be interspersed with those of anovulatory type, and vice versa, on the basis of scattered observations made by gynecologists, as well as on the basis of the more scientifically controllable studies on monkeys made by Hartman, Corner and others.

THE ENDOMETRIUM

The possible variations in the terminal menstrual life appear to have an influence on the postmenopausal histology of the endometrium. The best illustration of this is seen in the frequent finding (14), long after the cessation of menstrual function, of a typical Swiss-cheese pattern of the glands, exactly like that seen with the hyperplasia of the endometrium found in so many women toward the end of menstrual life, except that the picture is a retrogressive rather than an active one (figs. 1 and 2). Hyperplasia represents an exaggerated growth response in the endometrium, affecting both epithelial and stromal elements. It is a more or less stationary and non-cyclical histological picture.

With the onset of the menopause, however, the growth stimulus is removed. The stromal cells retrogress and may ultimately become fibrotic in appearance and the epithelial cells no longer exhibit mitotic evidence of active growth. But the gland pattern may continue for years to be of the Swiss-cheese type. Many of the glands remain large and cystic and I believe that this fact is the explanation of the cystic glands which for so many years, long before we knew anything of hyperplasia, have been described as common in the senile endometrium (fig. 3). Such cystic glands have in the past been assumed to be the result of cicatricial blockage of these ducts but this view is not supported by histological studies. On the other hand, the study of large numbers of hyperplastic endometria encountered in women from the active menarche to all ages beyond this epoch will reveal all phases of transition between active hyperplasia, retrogressive hyperplasia and senile endometria with cystic glands.

If this general conception is correct, one would probably be justified in assuming that the terminal cycles of menstrual life had been nonovulatory if one finds the hyperplasia stamp still present on the retrogressive endometrium of the woman long after the menopause. It is probable, though it cannot as yet be considered as established, that the endometrium of the woman who ovulates to the end of menstrual life will later exhibit the simple atrophic picture which has been traditionally associated with the senile phase (fig. 4).

However, it must be remembered that the endometrium of the post-menopausal woman is subject to the influence of post-menopausal estrogen stimulation, now a well-established possibility. We need not here discuss the source of this post-menopausal estrogen, except to say that the weight of evidence indicates it to be extra-ovarian, probably from the adrenal cor-

tex. Thus we not infrequently find typical hyperplasia, identical with that seen so often in the reproductive epoch, in women far beyond the menopausal age, even as old as 80 (14–16) (figs. 5 and 6). From a clinical standpoint, these cases may be associated with postmenopausal bleeding, a rather paradoxical type of functional bleeding, long after the cessation of functional activity in the ovaries. A considerable group of such cases has been observed.

After the menopause, as before, the endometrium appears to vary in the degree of its sensitivity or its refractoriness to the estrogenic stimulus and these variations are often seen in different parts of the same endometrium. Just as in the reproductive epoch one may find large areas of unripe or immature endometrium in an otherwise fully functioning mucosa, so one may find in a senile retrogressive endometrium localized areas of what is apparently typical and active hyperplasia. Not infrequently these localized areas are polypoid, just as one often finds polyps of hyperplasia pattern in a progestational endometrium during reproductive life.

Still another possibility after the menopause is the finding of a secretory endometrium, though this is very rare. Such an endometrium is ordinarily looked upon as evidence of a preceding ovulation, so that it might be looked upon as paradoxical to encounter it after cessation of the menstrual function. Breipohl (17) describes the endometrium as secretory in three of his post-menopausal cases, but in only one of these does he mention the time which had elapsed between the last menstruation and the operation, this being one year. In the other two cases it was presumably less, since his series included patients in whom the last menstruation had occurred six months or more previously. In the 137 endometria studied by Novak and Richardson (14), no case was included unless at least one year had elapsed; in none of these was a secretory endometrium observed.

Summarizing these observations on the postmenopausal endometrium, the following histological pictures may be encountered.

(1) The thin, atrophic mucosa, so commonly spoken of as the senile endometrium. This is numerically the most frequent finding in women beyond the menopause.

(2) A mucosa of varying thickness, but not always very thin, showing the Swiss-cheese pattern of hyperplasia but obviously of inactive, retrogressive type. Many of the glands are cystic and distended, others small and atrophic.

(3) Active hyperplasia, either diffuse or, more frequently, in scattered patches, large or small, and not infrequently polypoid. Various combinations of the above patterns conditioned by different degrees of sensitivity or refractoriness are seen in different parts of the same endometrium.

THE VAGINA

The loose generalization was formerly made that the estrogens are the growth hormones of all tissues of Muellerian derivation. The vaginal canal belongs to this group of tissues and it is certainly influenced by the estrogenic hormones, although we now know, as a result of the monumental studies of Robert Meyer (18) upon the embryology of the vagina, that its originally Muellerian epithelium is replaced at a relatively early stage of development by an epithelium derived from the urogenital sinus. Since the publication of Diercks (19) in 1927, there have been many studies directed toward elucidating the problem of the cyclical response of the vaginal epithelium to the ovarian hormones. While this question does not con-

FIG. 1. Retrogressed hyperplasia, with persisting cystic glands, seven years after the menopause, in a patient of 49 years. Note the fibrous type of stroma.

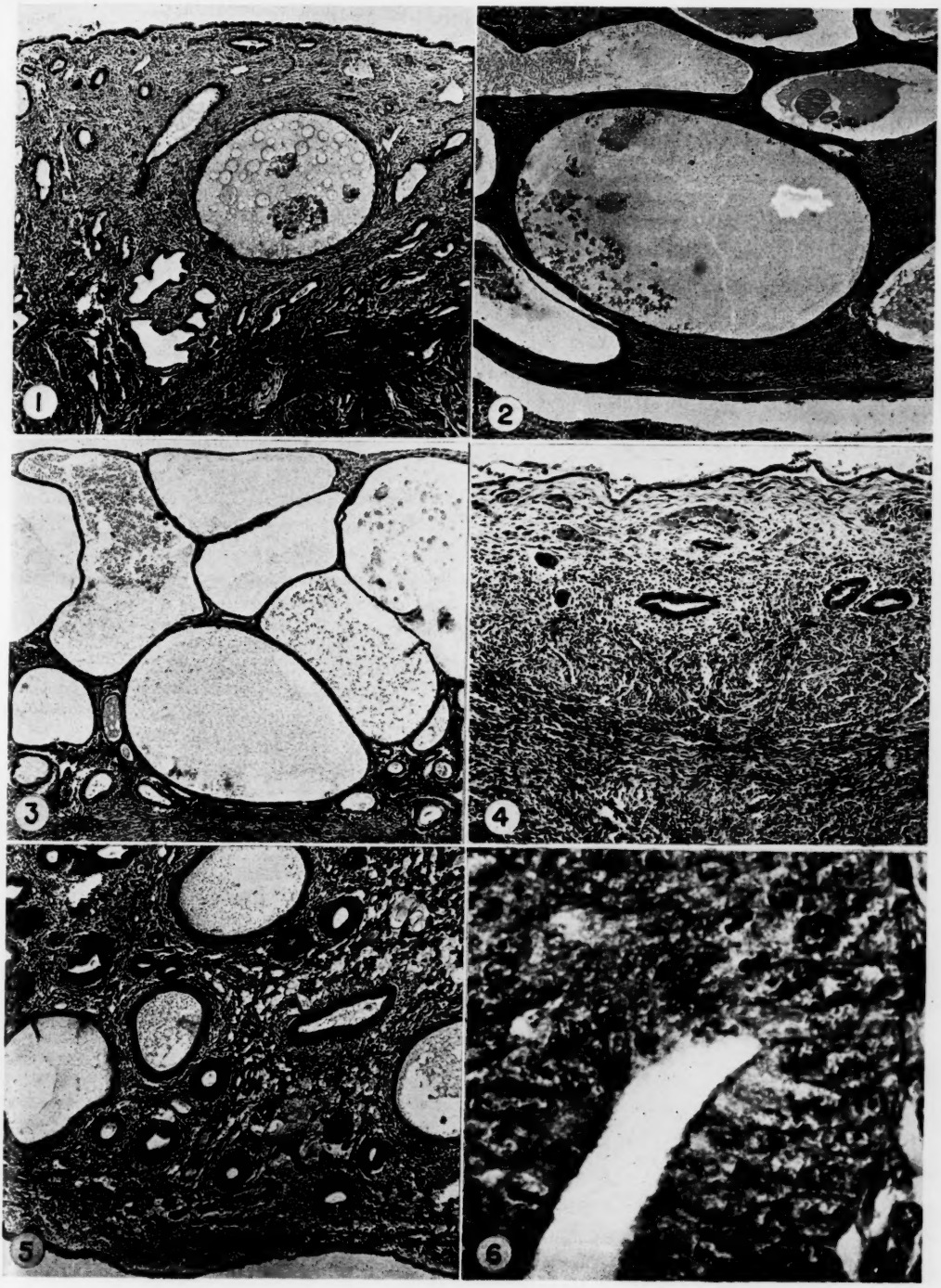
FIG. 2. Retrogressed hyperplasia ten years after the menopause, in a patient of 51 years. Note flat atrophic epithelium and fibrous stroma.

FIG. 3. Extreme cystic enlargement of glands, representing persistence of hyperplasia pattern (retrogressive) in patient of 57 years, three years after the menopause.

FIG. 4. Typical atrophic senile endometrium nine years after the menopause, in a woman of 58 years.

FIG. 5. Active, Swiss-cheese hyperplasia 30 years after the nenopause in a patient 80 years old. See high power of mitoses in epithelium (fig. 6).

FIG. 6. Mitoses in gland epithelium from another area of case shown in figure 5.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cern us in this paper, it is a curious fact that after all these years there is still a wide difference of opinion (20–22) on a question which would seem rather readily approachable by the simple histological study of a large number of biopsy specimens.

In more recent years, studies upon the hormonal reponses of the vagina have been carried out almost entirely by the vaginal-smear method, and this applies to both the reproductive and post-menopausal epochs. I do not believe that the vaginal-smear technique can give as accurate information concerning the histological variations in the vaginal mucosa as can be obtained from the direct study of biopsy specimens and this would certainly be true of the post-menopasual vagina. So far as I can find, no large scale histological studies of this sort have been made, and yet such a study should be of great interest, especially if it could be correlated, as it could be in many instances, with a study of the endometrium.

In view of the post-menopausal variations in the latter, it would be of value to determine whether similar histological variations are to be encountered in the vagina, although it cannot be assumed that the uterine and vaginal responses would necessarily go hand in hand. It is probable, however, that, as in the case of the uterus, the post-menopausal changes in the vagina are not always atrophic and retrogressive, and that evidences of post-menopausal estrogenic activity will at times be encountered in the vagina as in the uterus. We have recently become interested in this problem and hope to report upon it when a larger body of material has been accumulated.

SUMMARY

The anatomic changes in the endometrium of menopausal and pre-menopausal women are more or less the reverse of those seen at puberty and in early adolescence, particularly as to the relatively frequent occurrence of anovulatory cycles.

While the post-menopausal process is in general a retrogressive one, the post-menopausal endometrium is by no means always of atrophic type. Its histological variations appear in part to be imposed by the character of the terminal cycles, in part to the occurrence or non-occurrence of post-menopausal estrogenic stimulation, and in part, no doubt, to the degree of sensitivity or refractoriness of endometrial areas to this estrogenic influence. A number of these various histological pictures are described in the paper. While we have very little evidence on the subject, it is highly probable that similar variations, as a result of similar factors, occur in the histology of the post-menopausal vagina.

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The Aging Ovary—A Preliminary Note

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THE INITIAL plan for studying the menopausal ovary called for an extensive review of 500 case histories from patients 45 years of age and older, with a clinico-pathologic study of their ovaries. Such a study was more than half completed before the routine teaching and hospital duties, complicated by war-time lack of personnel, made it impossible to finish the work in time for this publication. The brief remarks to follow are therefore based on the day-to-day observations of a pathologist who sees the aging ovary as a part of a considerable volume of routine pathological material from a clinic devoted to elective gynecologic surgery.

It appears that the human female is endowed at birth with a certain ovarian "capital," namely, the primordial ova. In this author's experience, there are no new additions to such "capital" by way of oögenesis, either from the germinal epithelium or any other structures in the ovary. Thus the aging of the ovary, in one sense, really begins at birth and continues throughout life. Even as the menopause approaches, there are no abrupt changes in the ovaries of patients in their late thirties as against those in their early forties. Nor is there any abrupt change in the pre-menopausal as compared to the early post-menopausal organ. In this Laboratory we use the term "senescent ovary" to cover this transitional period, whether the patient be in the immediate pre-menopausal or post-menopausal age group.

In general, the aging takes place in an orderly and progressive fashion resulting in a gradual loss of primordial ova and their follicular phases, a progressive thinning of ovarian cortex which becomes increasingly wrinkled or gyrated, and a relative increase in the medulla which becomes the repository for corpora albicantia. The vessels of the hilum and medulla become progressively sclerosed.

It is fair to say that the age of the patient can often be rather accurately ascertained merely by an evaluation of these morphologic features in her ovary. To be sure, one is less accurate in such estimates when the menopause is fully established since the ovary then becomes a relatively static, although by no means an inactive, organ. This status is correlated with the impression held by some clinicians that a menopausal patient may experience a second menopause if her ovaries are removed surgically after the climacteric has been reached. Morphologically this would seem to be due to the presence of active-appearing cortex which may be present either as a thin regular layer beneath the germinal epithelium or as an irregular scalloped zone of cortical stroma about the periphery of the organ. The more active such ovarian cortices are, the more apt the patient is to have evidence of endometrial activity—ranging from inactive (though not atrophic) endometrium to hyperplasia of the latter tissue. Dr. George V. Smith, of this Clinic, has furthermore pointed out that the vast majority of patients with uterine cancer have an unusual degree of cortical stromal activity. This is merely another example of a probable utero-ovarian relationship in the genesis of endometrial cancer, the most striking one of which is the incidence in this Clinic of approximately 15 to 20 per cent endometrial carcinomata in cases of granulosa-cell tumors of the ovary (Smith's figures).

The increasing cortical gyration of the aging ovary, which usually begins in the early thirties, is often accentuated by areas of cortical stromal hyperplasia. In the depth of the sulci between such gyrations, one sees undisturbed germinal epithelium. Here the latter is cuboidal or even medium columnar in type—whereas on the surface of the gyri it is thin or

even absent. The latter is probably due to traumatic artefact. This increasing gyration is probably the factor which is largely responsible for the formation of germinal inclusion cysts. In this Laboratory, these structures, called "cortical glands," are believed to be the basis on which such common and diverse conditions as the cystadenomata, cystadenofibromata and endometriosis may develop, due to metaplasia of the now ectopic germinal epithelium.

In the age group of 45 to 49 years evidence of follicular presence, maturation and involution are usually encountered and therefore such patients usually show little clinical evidence of the menopause. The average midsagittal section of such an ovary shows only one or two primordial follicles remaining although some may show none at all. However, the latter ovaries will show evidence of follicular cysts or rarely an active corpus luteum. Small follicular cysts in moderate numbers are common during this senescent period possibly accounting for the menstrual irregularities which are so prevalent at this time. It is also during this time that mild degrees of cortical stromal hyperplasia are beginning to appear. Such hyperplasia is usually confined to the peripheral or cortical region but it may occur as a diffuse process throughout the erstwhile medulla. Such an ovary appears to be formed almost entirely of cortical stroma with, however, the usual corpora albicantia and vessels in the central portion.

After the age of 50 there is a rather striking loss of all phases of follicular activity. One only rarely encounters evidence of follicular activity, promordial or otherwise. There are, however, the relatively infrequent patients whose ovaries resemble those of a woman ten years her junior. Evidence of cortical stromal hyperplasia is more apparent in this group—especially in those with endometrial activity or outright malignancy.

In this Laboratory, we have encountered structures in the cortex of the menopausal ovary, and to a lesser extent in the senescent ovary, which we have termed "cortical granulomata." Other observers have doubtless seen them as well. They appear to be estrogenic in that their associated endometria show more activity than the age group would justify. They appear to start out as a single relatively large polyhedral cell or small group of such cells resembling the theca lutein type. They contain neutral fat as do the latter variety of cell. During the evolution of this "lesion" it becomes vascularized, attracts lymphocytes (as do involuting follicles on occasion) and finally ends up as a focal collection of multinucleated giant cells containing needle-like clefts—presumably from cholesterol deposition. More or less lymphatic response still remains about the periphery.

These "granulomata" do not appear to be inflammatory in the usual sense since there are none of the other stigmata of pelvic inflammation in these patients, nor are they formed in response to a foreign body—as for example, to talc from a previous pelvic operation. Whether they represent abortive attempts on the part of the ovarian stroma to carry on some sort of follicle-like activity in the absence of primordial ova is not clear. Suffice it to say, they are a definite morphologic entity which probably has some significance. Only further detailed and correlative studies will elucidate how this as well as the other aspects of the aging ovary fit into the general problem of menopause.

Cytology of the Anterior Pituitary Gland of the Post-Menopausal Woman

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THERE is abundant evidence both experimental and clinical that a close physiological interrelationship exists between the anterior lobe of the hypophysis and the ovaries. It is not surprising, therefore, that the pituitary gland should be suspected of playing some part in initiating the ovarian changes at the time of menopause. Carlson (1) expresses this point of view when he asks "if the waning of the gonads and the mammary glands is caused by an antecedent hypofunction of the pituitary?" He is properly cautious to point out that we do not have scientific evidence to enable us to answer this question. In fact, we cannot be sure whether changes in the functioning of the anterior lobe at the time of menopause result in the ovarian changes, or whether the pituitary alterations are the result of changes which for other reasons have occurred in the ovary.

Since it has been well established that cytological features in secretory cells give clues to the cell's activity, it should be worth while to study carefully the cells of the anterior lobe in the postmenopausal woman.

In this paper we shall describe a series of glands which were so fixed that such cell components as secretory granules, cytoplastic vacuolation, mitochondria and the Golgi apparatus are well preserved. These cell structures have already been studied in the pituitary glands of many species of animals and correlated with varying physiological states such as castration, pregnancy, thyroidectomy or hormone therapy (2).

The material consists of ten pituitary glands from women whose ages were: 35, 39, 46 (2), 49, 52, 58, 65, 73 and 74 years, and, for comparison, of nine glands from men whose ages were 36, 45, 46, 51, 58, 59, 67, 70 and 84 years. Through splendid cooperation of several institutions the glands were fixed in Champy's fluid (portions also in formol-Zenker and Bouin fluids) within an hour following death and thus the autolytic changes which so quickly set in after death were prevented. This is perhaps the chief virtue of the series which, although small, provides uniform material in which cytological details are preserved in cells which have not been distorted by varying periods of postmortem change. Sections were cut at 3μ and stained by methods previously described (3).

In the series of pituitary glands from women, we may select for description the anterior lobe of the woman sixty-five years of age. This individual was not only well past the age of menopause but actually in the old age group. The three cell types characteristic of the anterior pituitary gland, namely, acidophiles, basophiles and chromophobes were present. Although no cell counts were made to determine the relative percentages of these cell types, it was evident that the granular cells (acidophiles and basophiles) were present in abundance. These are the cells which elaborate the hormones.

The acidophiles were large and fully granulated. There were many cells in which mitochondria were large and abundant. There were cells in all stages of degranulation. Many cells showed a greatly enlarged Golgi apparatus. These cytological features are evidence that the acidophiles are in a state of active elaboration and discharge of their secretory product.

The basophiles were numerous and large and not markedly vacuolated. In the Champy preparations the basophiles showed a wide variation of coloration under the low power objectives, ranging from deep blue to a bright purplish-red. These differences were due to a

variable content of mitochondria and basophilic granules, a fact which could be shown by applying mitochondrial and copper hematoxylin stains to adjacent 3μ sections of the same cell mounted upon separate slides. Sections of Bouin-fixed material (a fixation which eliminates mitochondria) showed none of the tinctorial differentiations, although the great variation in the amount of basophilic granulation was again a striking feature. Many of the basophiles had a greatly hypertrophied Golgi apparatus. All of these cytological features indicate a high state of activity both in production and elaboration of secretory products by the basophiles.

A large body of cytological data indicates that the cytoplasmic granules in the acidophiles and basophiles are the precursors of the secretory products of the cell and that a varying degree of degranulation associated with an increased distribution of mitochondria is evidence of active secretory discharge from the cell. Likewise, a hypertrophy of the Golgi apparatus can be taken to indicate that the cell is actively elaborating its cytoplasmic granulation. The processes of elaboration and discharge may occur simultaneously, especially if the gland is in a state of active secretion. Such cells have a large Golgi apparatus as well as dispersed granulation and abundant large mitochondria. By these cytological criteria, therefore, the anterior hypophysis of this 65-year-old woman must be considered to be highly active in the production and release of some secretory product. There is no structural evidence whatsoever to indicate a state of hypofunction, which is so frequently associated with old age. The hypophyses of the other post-menopausal women were similar to the one selected for description, but showing varying degrees of increased activity.

Contrast now the anterior lobe of a man in a similar old-age group. There is at first glance an obvious reduction in the number and size of both granular cells. The basophiles which are present are filled with vacuoles. The chromophobes are plentiful. The cells have lost a compact arrangement, characteristic of the normal parenchyma, and are widely dispersed by an increased amount of connective tissue, colloid vesicles, and clear tissue spaces. The cells appear inactive, and have none of the cytological features which characterized the active, healthy cells described above in the female. Judged by its structural features this male hypophysis shows every sign of retrogression and extreme hypofunction. The structure of the anterior lobe in the human pituitary gland of the male and female in the old-age groups in these two instances indicate a marked sex difference in their secretory activity.

A study of the other glands in the two series shows that there is a progressive series of retrogressive changes in the pituitary structure with the onset of old age. These changes occur in both old men and old women, although there are individual differences in the degree of the changes and the time of their onset. With old age Rasmussen (4) has found that there is a significant increase in chromophobes and a decrease in acidophiles in both men and women above the age of fifty years. In women he finds a perceptibly higher percentage of basophiles but this is not true in older men. Parsons (5) has reported also that there is an increase in chromophobes (neutrophiles) and of connective tissue and that vacuolization of the acidophiles (eosinophiles) and basophiles is more prominent. In our series no attempt was made to determine the relative proportions of cells by differential cell counts, but we believe that actual counts would support the finding that chromophobes, to which we attach no secretory function, are increased and chromophiles are decreased with advancing age. Thus the basic or fundamental structural change associated with aging indicates an increasing hypofunction of the gland.

The extreme cases closely simulate the cell changes seen in the anterior-pituitary glands of rats which have undergone experimental inanition. They are also strikingly similar to the structural alterations seen in Simmonds' disease (pituitary cachexia). There are, in addition, features which are characteristic of the modifications caused by castration and thyroidectomy. It seems evident, therefore, that in the pituitary glands of aged individuals, at least two variable and modifying factors may always be present, namely, some degree of physiological castration and inanition, and that they produce their effects upon the cells.

Of what significance, then, is the present series of human pituitary glands studied by cytological methods to the problems of menopause? It is that we see in the hypophyses of post-menopausal women, not the usual structural changes which come with age and indicate progressively increasing hypofunction, but instead a gland which gives evidence of secretory activity even greater than in the period of maturity preceding the menopause. In this activity both acidophiles and basophiles are involved and we must ascribe to the cells a heightened rate of elaboration as well as release of their secretory products. This reversal in the usual trend of changes which come with increasing age has not been found in the hypophyses of men or in those of either sex of other species which have been studied. The positive finding in even a small series would thus seem to be significant.

Structural evidence of increased secretory activity of the anterior lobe at this time is in keeping with the presence of larger quantities of hormone, presumably of pituitary origin, which may be recovered from the urine of menopausal women. One would suspect, moreover, that, since both acidophiles and basophiles are involved in high activity, it would be difficult to infer the discontinuance in the production of any given hormone. This would bear out the experimental results of Nürnberger (6) and may have some bearing upon explanations of the menopause, such as that of Englehart (7), which suggests the disappearance of the luteinizing hormone as the cause of menopause. It would seem unjustified at this time to offer any interpretation of the menopause on the basis of these cytological studies and we should content outselves merely to state the facts, hoping that in the future they may somehow fit into the larger body of data from which interpretations can naturally follow.

SUMMARY

A series of pituitary glands from post-menopausal women were fixed by methods which preserve those cytological features in the cell which can be correlated with secretory activity.

A study of these glands in comparison with those of men and women of all age groups from maturity through old age reveals that the anterior lobe of the hypophysis in the post-menopausal woman is hyper-active in the production and release of its secretions. This is in contrast to cytological evidence of a progressive hypofunction normally associated with ageing.

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Hormonal Relations of Menopausal Symptoms

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THE CLIMACTERIC and the menopause result from a radical change in the endocrine system of the human female; and since all the endocrine glands are intimately linked in their physiologic action it is inevitable that they should be affected in one way or another. The exact mechanism by which this revolution is brought about is not known but studies of the past two decades have shed some light on the function of the anterior hypophysis with its gonadotrophic elements as well as of the ovaries and their estrogenic and progestin factors. This review deals solely with these tangibles, although the adrenals and the thyroid must be kept in mind as organs which also may play important roles or be subject to radical influences not as yet clearly understood.

OVARIAN HORMONES

During the active reproductive period of a woman's life the ovaries naturally play an important part and in addition to the formation of ova they produce two types of hormones which have specific effects on the uterus and the accessory genital organs. First are the estrogens which are concerned with the proliferation of the endometrium during the first part of the menstrual cycle; they appear in the blood and urine at a maximal concentration at about the time of ovulation with a secondary rise shortly before the appearance of the menses. Second is progesterone, the specific hormone of the corpus luteum, which promotes the qualitative changes of the endometrium necessary for the successful implantation and nidation of the fertilized ovum. This substance is not demonstrable in the blood or urine owing to its small concentration but it is excreted in the urine as a biologically inert substance called pregnanediol.

With the complete cessation of ovarian function which occurs following castration or the menopause, corpora lutea are naturally not formed and consequently it is not possible to demonstrate the presence of pregnanediol in the urine. Since estrogenic substances are considered as ovarian hormones it was once assumed that they likewise would not be found either in the urine or in the blood and, in fact, early studies indicated that this was the case (Frank, 1; Zondek, 2; Kurzrok, 3; Albright, 4). However, with the development of more efficient methods of extraction as well as of more delicate tests, it has been shown that estrogenic hormones are present in both the blood and the urine of a large percentage of post-menopausal women (Zondek, 5; Kurzrok and Ratner, 6; Frank *et al.*, 7; Fluhmann, 8; Eng, 9; Nathanson *et al.*, 10). The amount of hormone which has been found in these individuals is considerably less than that occurring during the reproductive period of life but it is of interest that Fluhmann and Murphy (11) observed a cycle in its appearance in 15 out of 27 instances.

The demonstration of appreciable quantities of estrogenic substances in the blood and urine of post-menopausal women is puzzling because it is co-existent with atrophic changes in the vagina, uterus and breasts. A number of explanations have been advanced to account for their presence. It has been suggested that atrophic ovaries may retain the power to produce a certain amount of estrogen but this can scarcely be accepted as the final solution since these substances also are found following irradiation-castration and surgical removal of both ovaries. For that reason, an extragonadal source of estrogen has been sought by various investigators and it has been thought by Parkes (12) and others that the adrenals may be the organs responsible.

The recent work of Emmens (13) demon-

strating the existence of certain "pro-estrogens" is of interest in this regard. He found that some synthetic compounds are comparatively inactive when applied locally to the vagina but develop markedly enhanced estrogenic properties when they have been absorbed into the general circulation and have undergone a metabolic transformation. The question arises, therefore, as to whether the human castrate and post-menopausal woman may or may not excrete certain "precursors" which are changed to true estrogens in the experimental animal. For the present it remains merely a theoretical possibility and the evidence is against it since the test animals employed are themselves castrates.

GONADOTROPHIC HORMONES

Of even greater interest than the diminution or complete cessation of the production of estrogenic hormones following castration or the menopause are the changes associated with the anterior hypophysis. As early as 1908 Tandler and Gross (14) demonstrated an enlargement of the sella turcica of eunuchs by means of x-ray studies, and histologic changes were described by Kon (15), Kolde (16), and Rössle (17). More recently Biggart (18) concluded that the basophilic cells of the hypophysis of the human castrate are increased in number and become prominently vacuolated. Since Severinghaus (19) recorded essentially the same findings in the pituitary glands of women in the sixth and seventh decades it appears that they normally occur following the physiologic menopause.

Along with these anatomic variations there is a tremendous increase in the amount of gonadotrophic hormones present in the blood and urine. The Aschheim-Zondek test, modified in one way or another, affords a simple procedure for their demonstration and in 1929 Fluhmann (20) showed that comparatively large quantities are present in the blood serum of castrates and post-menopausal women, while Zondek (21) found that they were also excreted in the urine. These observations have received confirmation from many sources (Mazer and Hoffman, 22; Jeffcoate, 23; Mazer and Andrussier, 24; Brühl, 25; Österreicher, 26; Zondek, 27; Gostimirove, 28; and others). This remarkable increase of gonadotrophins, which may amount to more than twenty times normal quantities, often makes its appearance before the menopause, the actual cessation of menstruation (Fluhmann, 29; Fluhmann and Murphy, 11 and 30). It may disappear following a temporary amenorrhea due to x-irradiation of the ovaries (Nathanson *et al.*, 10), and it has been seen to persist into old age (Österreicher, 26).

It seems established beyond doubt that the gonadotrophins found in the blood and urine following castration or the menopause originate in the anterior hypophysis. In addition to the increased size and histologic changes of this organ, there is evidence from animal and human studies that after castration or the menopause in women it has a greatly enhanced potency when implanted into experimental rodent animals (Engle, 31; Evans and Simpson, 32; Henderson and Rowlands, 33; Noble *et al.*, 34). The histologic changes elicited in the ovaries of immature or hypophysectomized mice or rats by blood or urine also are identical to those produced by extracts or implants of the anterior lobe (Leonard and Smith, 35; Hamburger, 36; Fluhmann, 37 and 38). These effects are chiefly a growth of graafian follicles due to the anterior lobe "follicle-stimulating" hormone and the formation of corpora lutea induced by the "luteinizing hormone." Following the injection of blood or urine from castrate or post-menopausal women the predominant result is a growth of follicles, although luteinization sometimes occurs (Fluhmann, 20). This picture is in startling contrast to that produced in the rat by the chorionic hormone, which picture is characterized by large corpora lutea and relatively fewer developing follicles.

The exact mechanism which brings about the production and excretion of these large amounts of gonadotrophic hormones is not known but two schools of thought exist. Some maintain that there is an actual overactivity of the hypophysis due to the removal of an inhibitory or regulatory function of the ovaries. Others, on the other hand, contend that the increase of hormone noted in these women is simply due to non-utilization (Heller *et al.*, 39), a concept which receives some support from experimental observations of Seidlin (40).

RELATION OF ESTROGENS AND GONADOTROPHINS TO CLIMACTERIC SYMPTOMS

There has been considerable discussion as to the exact relationship between the estrogenic and gonadotrophic hormones and the development of climacteric symptoms. The diverse opinions of various investigators fall into three main groups.

I. It has been suggested that climacteric symptoms may be caused directly by the overproduction of gonadotrophins (Albright, 4; Kurzrok and Smith, 41; Nathanson *et al.*, 10; Lawrence and Moulyn, 42) and support for this concept is found in studies which demonstrate a relationship between the amount of hormone in the blood and urine and the severity of the patients' complaints. Although Heller *et al.* (43, 44) recently could find no correlation between these two factors, Albright (4) observed that as the titer of the urine tests increased the number of hot flushes occurring in individual patients likewise rose. Fluhmann and Murphy (11) divided a series of patients according to the severity of symptoms and found that in the group with mild manifestations an increase of anterior-lobe hormone in the blood occurred in 53 per cent of instances. In another group, in which hot flushes occurred more frequently, positive tests were found in 76 per cent, while they were present in 100 per cent of the cases with the severest degree of symptoms. An interesting observation recorded by Lawrence and Moulyn (42) is that vasomotor disturbances dominated the clinical picture in 81 per cent of their patients with positive tests for gonadotrophins as compared to only 15 per cent in those with negative tests.

There are, however, several objections to accepting the theory that excessive production of gonadotrophins is the direct cause of climacteric symptoms; these recently have been reviewed by Heller *et al.* (44). (1) Although it has long been known that the administration of large dosages of estrogenic substances may diminish gonadotrophic activity (Albright, 4; Frank, Goldberger and Salmon, 45; Salmon and Frank, 46; Fluhmann and Murphy, 11 and 30), the use of amounts too small to affect the titer of anterior-lobe hormone in the blood or urine may yet result in amelioration of symptoms (Albright, 4; Fluhmann and Murphy, 29; Heller *et al.*, 45). (2) An increase of gonadotrophins has been observed in climacteric women without symptoms (Heller *et al.*, 44) and in other cases this increase may appear before the onset of hot flushes. (3) Prepuberal gonadal failure associated with a high urinary output of gonadotrophic hormones is not characterized by climacteric symptoms in either males or females (Heller *et al.*, 44). (4) An increased amount of the hormone has been seen in some instances of amenorrhea of long duration not associated with the occurrence of vasomotor disturbances (Fluhmann 47). (5) Climacteric symptoms were not encountered in the women with primary amenorrhea, short stature and high gonadotrophins described by Varney, Kenyon and Koch (48) and Albright, Smith and Fraser (49). (6) They also do not occur in males suffering from the syndrome reported by Klinefelter, Reifenstein and Albright (50) in which high gonadotrophin and normal 17-ketosteroid values co-exist. (7) Heller *et al.*, (44) have observed the presence of climacteric symptoms in three cases of gonadal deficiency secondary to pituitary failure, in which excretion of gonadotrophic hormones was below normal (8). Improvement of climacteric symptoms has been achieved by such means as the administration of sedatives and x-irradiation of the hypophysial area of the skull, which do not diminish any existing increase of anterior lobe gonadotrophin in the blood (Fluhmann and Murphy, 11; Geist and Mintz, 51).

II. The second theory which offers an explanation for the development of climacteric symptoms is that they are brought about by the disappearance or decrease of estrogenic hormones. The reasons advanced for this explanation are mainly two (Heller *et al.*, 44). In the first place, the symptoms occur when evidence of ovarian failure, such as atrophic changes of the accessory genital organs, is invariably present. Second, symptoms are promptly and specifically relieved by estrogenic therapy.

There are several objections to accepting estrogen withdrawal as the sole factor concerned in the production of climacteric symptoms. As noted previously, the presence of estrogen can be demonstrated in the blood

and urine of a considerable number of postmenopausal women but no correlation has been established between the amount of hormone present and either the existence or absence of symptoms (Shute, 52) or their severity (Frank *et al.*, 53; Fluhmann and Murphy, 11; Lawrence and Moulyn, 42). Climacteric symptoms may appear before menstruation actually ceases and it must be assumed that during this period adequate amounts of estrogen are available to the individual. Albright (4) feels that hypo-estrinism is not the direct cause of the vasomotor phenomena resulting from castration or the menopause because "(a) with oöphorectomy estrogen disappears long before the hot flashes begin; (b) during the menopause, the estrogen level can be brought with estrogen treatment above normal for a long period of time before the hot flashes cease; (c) hypo-estrinism due to pituitary disease is not accompanied by hot flashes."

III. It is thus seen that serious objections exist to considering either the increase of gonadotrophins or the disappearance or diminution of estrogens as the direct cause of climacteric symptoms. For this reason it appears necessary to consider two other possibilities. First, one of these two hormonal changes may be responsible but only indirectly by affecting one of the other glands, possibly the adrenal, which in turn induces the systemic reactions. Second, the symptoms and these endocrine manifestations may not indicate a "cause and effect" relationship but both features may result from some as yet unrecognized basic cause (Fluhmann and Murphy, 11).

EFFECTS OF THERAPY ON HORMONAL FACTORS

The administration of estrogenic substances in adequate dosages inevitably raises the amount present in the blood and urine of climacteric women; and results not only in amelioration of the various systemic disturbances but also of the local atrophic changes. In addition, there may be a profound effect both on the anterior hypophysis and on the titer of gonadotrophins in the blood and urine. Rowlands and Sharpey-Schafer (54) found that the daily administration of 10 mg. or 100,000 I.B.U. of estradiol benzoate for periods lasting from three to 54 days resulted in a decrease of the content of gonadotrophic substance as assayed on the hypophysectomized rat. It is likewise possible to cause a marked diminution in the amount of gonadotrophins present in the blood and urine but large dosages of estrogen are essential. Albright (4) gave as much as 2000 I.U. of estrogen ("Progynon") orally daily in order to cause a disappearance of excessive gonadotrophic hormone in the urine, while Salmon and Frank (46) employed a total dosage of 11,000 to 14,080 units of estriol glucuronide ("Emmenin") and Jones and Macgregor (55) 500,000 to 1,500,000 I.U. of estrin ("Dimenformon") to accomplish the same result. Fluhmann and Murphy (11) found that 60,000 I.U. of estrogen ("Amniotin" or "Progynon-B") resulted in a disappearance of unduly large amounts of gonadotrophin in the blood serum of only two out of six women. As pointed out previously, climacteric symptoms may be alleviated by the use of sedatives, x-irradiation of the hypophysial area or small dosages of estrogen, which do not affect the titer of gonadotrophins.

SUMMARY

With the cessation of menstruation, at the menopause, there are two important changes in the hormones concerned with reproduction. The atrophy of the ovaries results in a disappearance of estrogenic substances from the blood and urine in most instances but they are still demonstrable in diminished amounts in a certain percentage of cases. There must consequently be some extragonadal source, possibly the adrenals, for this hormone.

The loss of gonadal function leads to an increased gonadotrophic-hormone content of the anterior hypophysis, and marked increase of the gonadotrophins in the blood and urine.

These hormonal changes have each been suggested as the direct cause of climacteric symptoms. There are, however, distinct objections to accepting either the disappearance or diminution of estrogen or the increase of gonadotrophins as the immediate factor concerned.

The administration of large dosages of estrogen may result in a diminished gonadotrophic-hormone content of the anterior lobe as well as a disappearance of excessive quantities from the blood and urine. However, symptoms may

be ameliorated by small dosages of estrogen, by sedatives or by x-irradiation of the hypophysial area without affecting the amount of gonadotrophin present.

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Medical Therapy During the Menopause

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The menopause is the absence of menstruation due to physiologic cessation of ovarian activity. It normally occurs between the ages of 40 to 50 years and any cessation of menstruation previous to that must be suspected of having pathologic etiology or to be due to pregnancy. In so far as is known at present, the only actual symptoms resulting from this physiologic ovarian inactivity are amenorrhoea and vasomotor instability characterized by hot flushes. Therefore, we must assume that the multitudinous other symptoms from which women suffer at this stage of life are subjective and due to something beside physiologic cessation of ovarian activity. In any consideration of the treatment of the menopause it must be remembered that these secondary symptoms are frequently the complaint for which the patient demands treatment. Therefore the theoretical purpose of menopausal therapy—*i.e.*, the substitution of ovarian function by therapy with estrogens, is frequently either unnecessary or inadequate. These symptoms, as identified in a critical analysis on 1000 women (1), were headaches, dizziness, "nervous instability," in decreasing proportions from 45 per cent to 30 per cent, and other vague and isolated symptoms. This is roughly similar to the usual experience in treating menopausal patients. What, then, is the actual source of these elusive and troublesome symptoms? This source we assume to be the "climacteric," which literally translated means "rung of a ladder." The "climacteric" was originally and now could presumably be used as a definition of a significant period in anybody's life, but it has come to be conventionally used to cover that time in the life of a woman when her fertility is disappearing and menstruation ceasing. Because of tradition, folklore, and idle uncritical chatter, this period is approached by many women with considerable dread. Therefore, is it any wonder that from a third to a half of them suffer from "nervous instability"? The actual cessation of menstruation brings realistically to a woman the undeniable fact that she is aging, that her reproductive potentialities are leaving her and that she has therefore fulfilled her physiologic usefulness in life. When surveyed from this viewpoint, it may be considered surprising that even more women do not have symptoms.

There have been, however, numerous and varied attempts made to correlate all these symptoms of the climacteric with definite physiological changes in the organism—with very confusing results.

Although Fluhmann and Murphy (2) could find no relationship between estrogen excretion and the occurrence of flushes, Watson *et al.* (3), treating patients more on a basis of levels of excretion of estrogens and androgens than on symptoms, got very good therapeutic results in 28 cases. Noticing that menopause patients excreted large amounts of gonadotropic hormone, both Fluhmann (2) and Albright (4) found a relationship between flushing and this excessive gonadotropic excretion. On the other hand, Heller, Farney and Myers (5) found that surgical castrates developed urinary gonadotropin titers of a menopausal level within six to ten days postoperatively, whereas they did not develop menopausal symptoms for from 27 to 66 days. They assume that this discrepancy in time relationship is an indication that there must be another factor, or factors, involved in the onset of symptoms.

Whether or not the atrophic changes which

occur in the genital tract are in any way related to menopausal symptoms—or whether they have a similar etiology—is an undecided question. McLaren (6) observed some correlation between the atrophic appearance of the epithelium in vaginal biopsies and the onset of menopausal symptoms but Salmon and Frank (7) could find no definite association between these two.

Reynolds (11) has made an intensive attempt to ascertain exactly what hot flushes really are—but he, like others, found it almost impossible to separate actual physiologic changes from subjective symptoms. Selecting for research purposes 18 women who complained of severe flushes, and *flushes only*, he found that 11 did not respond to estrogen therapy satisfactorily, but did respond after a thorough investigation disclosed psychic, economic or social conflicts which were properly treated and adjusted. It might reasonably be asked why these symptoms should have occurred concurrently with the menopause unless there were some relationship.

It is probable that these patients had somewhat the same psychiatric, economic and social problems before this menopausal epoch, but compensated for them. The added psychic insult of the climacteric is the trigger mechanism which may upset a previous adjustment. In many cases the menopause is used as an excuse for, or a sanctuary from, an intolerable situation.

It is also an undeniable fact that every woman who goes through the menopause undergoes physiological changes due to varying degrees of estrogen depletion—yet only a relatively small percentage have symptoms. Obviously there are more complex psychosomatic instabilities in some individuals than in others which probably makes them more sensitive to the period of life through which they are progressing.

It is therefore apparent that the "climacteric" is a condition with many facets—only one of which is estrogen depletion. As Ross (8) says, it cannot be called a disease, unless the process of aging is called a disease; yet the insecurity, instability, depression and introspection which frequently accompany this period of life must be treated.

TREATMENT

It should hardly seem necessary to say that the most important factor in the treatment of the climacteric is a thorough history and physical examination. Unfortunately, however, practically any symptoms of which a woman between 40 and 50 complains are too often attributed to the menopause until proved otherwise. And the proof is unfortunately too often a sudden aggravation of symptoms which identify a serious disease which, with a little care, could have been diagnosed earlier and the patient properly treated, instead of receiving irregular and various dosages of different estrogens. Every clinic treating menopause cases can provide many examples of this situation as exemplified in the following case:

Naval Academy Dispensary No. 1922—*M.S.* Age 41—The patient came to the dispensary because she wanted "theelin injections." She had been receiving these for six to eight months once a week elsewhere but, because her husband was in the Navy, came to the dispensary for treatment. She was originally given the treatment, she stated, because she was suffering from headaches and hot flushes. She had had an operation several years before resulting in an artificial menopause and had gained about 30 lbs. since then.

Physical examination disclosed an obese woman with flushed face but apparently in good health. Her blood pressure, however, was 230/140 and an electrocardiogram showed a left axis deviation. A diagnosis of hypertensive cardiovascular disease and obesity was made and the patient was treated with a reducing diet, sedative, rest, etc. She lost 40 lbs., her blood pressure was reduced to 170/90 and her symptoms disappeared.

The tendency to treat women at the climacteric age with estrogens is a tempting one, but unfortunately these women are also susceptible to other physiological disturbances than estrogen depletion. Patients with diabetes, hypertension, and many other common or unusual diagnoses have been found to have received extensive estrogen therapy before their true pathologic lesions were sought and identified. That there may be a combination of these diseases with the climacteric is naturally possible, and with the metabolic diseases, probable. Therefore, following adequate history and physical examination, each case must be treated on its own merits.

Novak (9) states that one of the most important considerations in the management of the

climacteric is the elimination from the mind of the patient of the many legendary misconceptions concerning abnormalities which occur at this time.

McLaren (6), in fact, is of the opinion that weight increase, for instance, commonly thought to be due to metabolic changes accompanying cessation of ovarian secretion, is in most cases actually due to carelessness in diet—this carelessness being produced by a tendency of women at this age to let down on their general appearance. Loss of libido, frequently picturesquely designated as "change of nature" by the layman, is another common apprehension which is much more psychological than physiological, as it is a well known fact that some women may have an actual increase, rather than a decrease, in libido following the menopause. Sympathetic conversation with women at this period will often elicit confessions of other needless apprehensions from which they are suffering. By a practical psychological investigation and common sense discussion and treatment many of the preconceived fears and the uncertainty connected with the climacteric can be alleviated.

It is important, however, to identify the more severe underlying psychoses which may appear during the climacteric and place these in proper hands for intensive therapy. The present attitude among psychiatrists (Heaver, 10) concerning involutional melancholia, depressions, paranoid states, etc. that appear at this time is that they all have a previous history of psychiatric instability which the additional psychological strain of the climacteric brings into focus. Therefore these patients must undergo psychiatric therapy with this background in mind.

As the climacteric brings to light psychological and psychiatric abnormalities which had been previously quiescent or under control, so does this period of life seem to aggravate previously tolerable socio-economic-family problems so that they assume proportions intolerable to the patient. Thoreau's "life of quiet desperation" explodes under this added strain at its weakest point, and it is incumbent upon the physician, through appropriate facilities, to try to adjust these intolerable situations as well as possible—or at least adjust the patient to them. This factor is well brought out in the report of Reynolds' careful investigation of 18 women complaining of *flushes only*. Eleven of these, as previously stated, had socio-economic or psychiatric problems which were the basic source of their difficulties.

Medical therapy for the menopause has been varied and colorful. Hormonal treatment is said to have been used first in the Landau clinic in Berlin in 1896. Such a careful investigator as W. P. Graves stated years ago that corpus-luteum therapy was almost a specific in menopausal treatment—and the corpus-luteum extract used then is now known to be physiologically inert. Although the technique of estrogen therapy is discussed elsewhere, it is not out of place here to agree in the hearty condemnation of the use of dessicated whole ovary by mouth in the treatment of the menopause. This substance is also innert physiologically and should never be prescribed by the physician. Representatives of most drug houses state that the whole-ovary substance is extracted and distributed only because the profession demands it. If this is true, the profession is unconsciously using a lot of psychotherapy!

Following the elimination of all patients who, by history, physical examination and laboratory findings, are found to be suffering from conditions other than the menopause, the remainder are placed on mild sedatives for an indefinite period of time. It has been the conventional technique in the endocrine clinic at the Sloane Hospital for Women to use barbiturates, especially phenobarbital, rather than bromides or other sedatives. Phenobarbital grains ¼, three times a day, about ½ hour before meals, and a grain at bedtime, completely relieves a large number of these patients. This is true especially if its use is abetted by considerate and encouraging suggestions and advice. The length of time necessary for continuation of treatment varies greatly—from a few weeks to a year or more.

Of 91 cases referred to the Sloane endocrine clinic with a diagnosis of menopause (fig. 1), 11 were found to have other pathological conditions which were thought to cause the symptoms elsewhere attributed to the climacteric.

These conditions are listed in table 1 and present a varied picture, emphasizing again the importance of a careful evaluation of a patient's history and physical examination.

The remaining 80 cases were started on a regime of phenobarbital as above described. Thirty-six, or almost half of these 80 patients, were either completely relieved of symptoms or so greatly relieved that they requested no further medication. The 44 remaining patients who had not been affected by sedation therapy were then given varying dosages of estrogen.[1] Of these 44 patients, 20 were either completely or almost completely relieved of symptoms whereas 24 found no benefit in estrogen therapy. These 24, therefore, had been given sedation and estrogen therapy at separate times but had been unaffected by either. Consequently phenobarbital and estrogen were administered simultaneously and seven of the 24 patients were relieved by this system of medication. That left 17 patients, or 20 per cent of the original 80 under treatment, who were unaffected by any treatment given them in the clinic. These patients, of the type to be found in every clinic dealing with menopause problems, probably fall into the category described by Reynolds as being women whose psychiatric and socio-economic problems are such that they are in need of thorough and intensive investigation.

It must be remembered that, contrary to the technique of most reported series, sedation as treatment was used *first* in these cases; those having no benefit from therapy then receiving estrogens. Without a doubt, many of those cases originally relieved by sedation would have been equally benefited by estrogen. The purpose, however of administering sedation first was to ascertain whether or not estrogen substitution must be used as *specific* therapy in menopausal treatment.

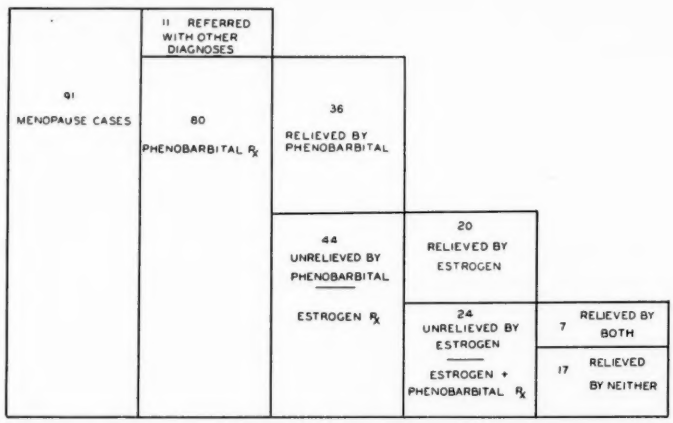

FIG. 1. Disposition and results in treatment of 91 cases of menopause syndrome at the endocrine clinic of the Sloane Hospital for Women.

TABLE 1

Medical reasons for referal of eleven women

2	Hyperthyroidism
2	Hypothyroidism
1	Aneurysm Internal Carotid Artery
1	Ophthalmological Disturbance—Undiagnosed
1	Obesity
2	Hypertension
1	Skull Fracture (Old)
1	Diabetes

Eleven patients, referred to the Endocrine Clinic, whose symptoms were thought to be due to above-listed disorders. Many menopause cases, of course, had concomitant, superimposed hypertension and obesity but were treated as menopause cases because symptoms were thought to be due to latter condition.

[1] For the most part these patients received diethyl or methyl stilbestrol. If these were not tolerated, estriol glucuronide, estrone sulfate or estradiol benzoate was administered. Except for the latter, all medication was given by mouth. No attempt was made to differentiate between the various types of estrogen used since this aspect of the problem has been adequately covered on numerous occasions elsewhere, and differentiation of estrogen potency was not the purpose of this study.

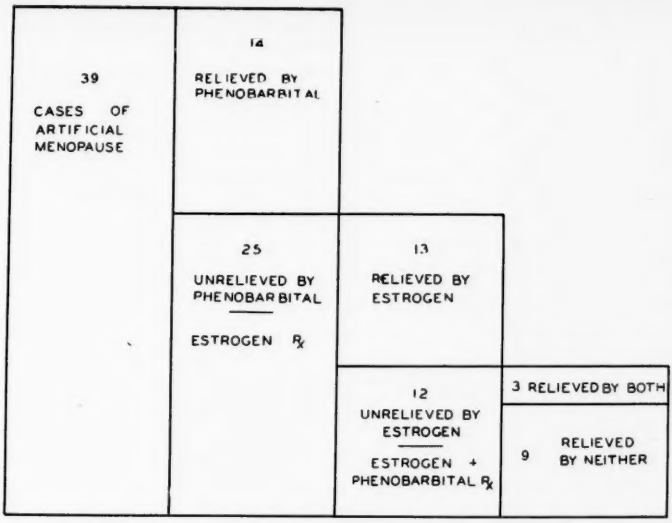

FIG. 2. Results of treatment of 39 cases of menopause syndrome produced by either radiation or surgical castration.

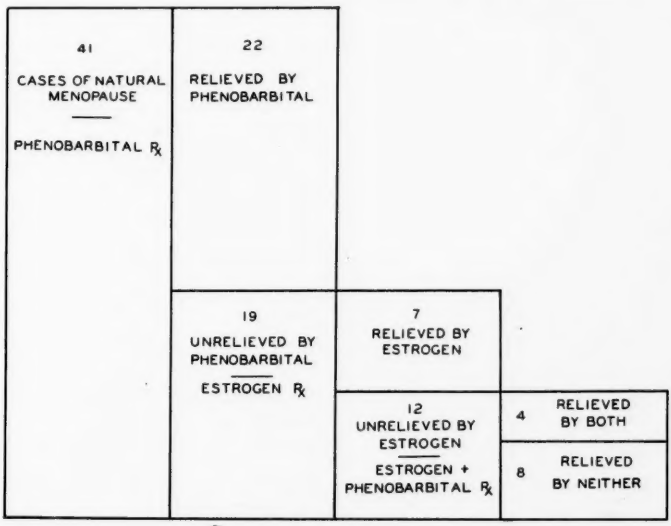

FIG. 3. Results of treatment of 41 patients with natural menopause.

Thirty-nine of the 91 menopause patients were of the artificial type—due to surgery or irradiation (fig. 2). As might be expected, a slightly smaller proportion of these were relieved or improved by phenobarbital. Of those suffering from the physiological menopause (fig. 3), slightly more than one-half were relieved or improved by sedation therapy.

SUMMARY

General considerations concerning the physiology of the menopause are discussed with a review of the attempts which have been made to correlate objective physiological changes with subjective symptoms. For the most part no relationship—or at best only a vague one—has been observed.

Ninety-one cases referred to the endocrine clinic of the Sloane Hospital for Women are reviewed. These patients *first* received sedation therapy consisting of small preprandial doses of phenobarbital. Forty-five per cent of these patients who received medication were either completely cured on this regime or were so relieved that no other medication was necessary. Even after estrogen therapy, or combined estrogen-sedation therapy, 20 per cent of the patients were unrelieved of their symptoms.

CONCLUSIONS

The climacteric is a condition involving more than estrogen deficiency.

Therefore the treatment of the climacteric is more complex than that of estrogen substitution.

Furthermore the majority of menopause patients do not require estrogen substitution therapy.

An appreciable number of patients are benefited by neither sedation nor estrogen treatment. They are probably in need of psychiatric care and socio-economic readjustment.

A menopause treatment regime is suggested consisting of sedation therapy *first*, followed by estrogen replacement if necessary.

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Therapy of the Patient in the Menopause: Endocrine Methods

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DIAGNOSTIC PROBLEMS

BEFORE undertaking treatment for the menopause syndrome it is important to insist upon certain diagnostic steps. Most obvious is the requirement that each woman who arrives at this period of readjustment should have a general review of her history and a systematic examination for the sake of her entire health problem. The extent to which this needs to be elaborated will depend upon the amount of detail about her which the physician already has available in his records. Specifically sought is evidence of neoplasm in the breasts or pelvic organs. Uterine fibroids or polyps may be a contraindication to estrogenic therapy or may require surgical treatment before estrogens are administered.

When menstrual irregularity, amenorrhea, or menorrhagia occur before age 40 they may be indications of the menopause occurring prematurely, but before treatment is started other possibilities should be given deliberate consideration. These phenomena may follow dysfunction of the ovaries induced not only by primary ovarian failure (the usual concept of the menopause) but also by anterior-pituitary or, occasionally, thyroid disturbance. In turn these latter may be induced by systemic disorders of varied types. If careful examination does not reveal systemic disease and if basal metabolism and serum cholesterol determinations fail to substantiate thyroid etiology, one is left to decide between pituitary and ovarian failure as the cause. In only a few experimental clinics is it possible to make assays of gonadotrophic hormone excretion in the urine. When this is significantly high ovarian failure is believed to be the cause of the anomalies of menstruation mentioned. If, on the other hand, pituitary gonadotrophic excretion is not elevated above normal levels, the ovaries may still be susceptible to stimulation by appropriate therapy with extracts from the anterior pituitary or from serum of pregnant mares. It is wise to attempt this differentiation whenever possible, for estrogenic therapy is not effective in stimulating ovaries, tending to reduce their activity (1). This diagnostic decision is especially important if fertility is an important objective.

OBJECTIVE

Treatment in the menopause, as usually in medicine, is directed to the relief of symptoms.

CLIMACTERIC SYMPTOMS	
Autonomic and Peripheral Nervous	Psychic
Irritability	Emotional instability
Hot flashes	Melancholy
Sweating attacks	Weeping
Chills	Morbid worrying
Palpitation	Insomnia
Dyspnea	Fatigue
Vertigo	Self depreciation
Headaches	Self accusation
Paresthesias	Jealousies
Pruritis	Suicidal thoughts
Hyperesthesias	

In other words the menopause does not require any therapy but the menopause syndrome may be well worth treating. A woman may be told frankly that she should decide whether the relief of symptoms is worth the time and the cost required to secure relief. She should be told that there is no adequate

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reason to reestablish menstrual flowing. In fact such flows usually represent imperfection in the timing or intensity of therapy. Except for psychological reasons it is doubtful that a woman is really more comfortable when she experiences flows. The apparent exceptions are probably due to the decrease in tension which accompanies a decrease in estrogen, produced by the ovaries or therapeutically administered, preceding by a very few days the onset of some flows. A corollary of these observations is that a large number of women pass through the menopausal period with so few symptoms that they need not have any specific treatment.

The discovery that gonadotrophic-hormone excretion in urine is increased during and after the menopause led some of the earlier students to the theory that the adequate dose of estrogen would be that which reduces such hormone excretion to the normal range. This has been shown to be erroneous (2). It is evident that symptoms of the menopause are not due to this excessive amount of gonadotrophic hormone, since the symptoms can be relieved without depressing the urinary hormone titer and since the hormone excretion continues at a high level for many years after the menopause syndrome has subsided, with or without therapy. The objective of therapy in the menopause syndrome is to minimize intensity and duration of symptoms. The intensity can be reduced to the vanishing point in almost all cases if treatment is adequate in amount and well planned in dosage. The duration of the syndrome is so variable that one can draw conclusions about any change in duration only on a statistical basis. Clinical experience shows that it is rare to have the symptoms persist after as much as five years of adequate use of estrogens, although it is not uncommon to have untreated women complaining of these discomforts for ten to twenty years. It is highly probable that proper methods will reduce the duration of discomfort as well as ameliorate the syndrome throughout its course. There is certainly no good evidence indicating that after use of estrogens the woman must look forward to having to undergo a transition period with symptoms, or else continue treatment for the remainder of her life.

ESTROGENIC MATERIALS

Of the ovarian hormones only those with estrogenic potency appear to be helpful in relief of the menopause syndrome. Of these naturally occurring hormones (steroids) the one known as estradiol is most potent per milligram but is also most labile when introduced into the body. It is probably the original material produced in the ovaries. Two of the more important products made by several tissues from estradiol are estrone and estriol. These are of lower potency per milligram, are correspondingly more stable, and have therefore been more widely used clinically.

The only commercially available preparations of estradiol are synthetic materials, which are administered in this form orally, or as esters in oil solution intramuscularly. The benzoate, propionate, and palmitate have all been used with effect. Estrone and estriol are secured commercially from urinary sources, either human or equine. They are prepared in crystalline purity. Either may be used orally or by intramuscular injection in oil. Hypodermic administration of aqueous solutions has been abandoned because of the low solubility of these substances in water, with consequent limitation of the size of the convenient doses. Since it has been so widely assumed that estrone is not effective orally there are no commercial preparations of this agent available for oral treatment. For oral use estriol has been suggested. Estriol is so low in its clinical efficiency that estrone is greatly to be preferred (3). It is not at all necessary that these estrogens be prepared in a state of purity such as leads to crystallization. There are in use several preparations which contain chiefly estrone, with very small amounts of estriol and of other weakly active, naturally estrogenic compounds. These are manufactured from urinary sources, accurately standardized against pure estrone, and have clinical characteristics essentially like those of pure estrone (3). These preparations are now used under the generic term "Estrogenic Substances," adopted by the Council on Pharmacy and Chemistry of the American Medical Association. Recently a further step in modifying the preparation has been introduced by one manufacturer in al-

lowing estrogens to remain conjugated with potassium sulfate as they occur in urine. This renders them more readily water soluble in the finished product, which in this case is used orally exclusively (4). The other estrogenic substances may be given orally or by injection. Another recent modification has been the preparation of aqueous suspensions of very finely divided estrone or estrogenic substances, for injection without the use of an oil vehicle.

The androgenic hormone of the testis, testosterone, has been reported to be effective in relief of the menopausal syndrome (5). The risks of virilizing effects, greater cost, and the debated efficiency make it appear unwise to advise further trials of androgenic hormone in treating the menopause syndrome, especially since this can be managed so adequately by estrogenic materials.

Synthetic preparations with typical estrogenic activity are numerous. Only four have come into wide clinical use and commercial production. Of these the most widely employed is diethylstilbestrol, commonly known as stilbestrol. A simple derivative is called dihydrostilbestrol or hexestrol. An interesting variation on this molecular structure is called methyl ethyl stilbestrol, or monomestrol. The fourth compound is radically different, known as benzestrol, and first marketed under the term "octofollin." All these compounds are about as effective when given orally as when injected in oil solution or in an aqueous suspension. Their potency per milligram is greatest in the case of diethylstilbestrol, least for benzestrol. Advantages shared by all these synthetic estrogens include lower cost than the naturally occurring compounds and little loss of effectiveness on oral administration. The synthetic materials also share a common disadvantage of causing unpleasant side reactions. The commonest is nausea, and this probably serves as a deterrent to such therapy in not more than 20 per cent of women. There is no evidence of more serious or of any permanent toxicity to therapeutic doses of these compounds. The choice between natural estrogens (steroids) and synthetic materials is usually dictated by cost (in favor of the synthetic) unless nausea or other unpleasant sequellae lead to use of the natural hormone products.

ROUTES OF ADMINISTRATION

Both steroid and synthetic estrogens are in wide use as oil solutions injected intramuscularly. In order to prolong the activity still further than by the slow diffusion out of the oil into the tissue fluids, these estrogens are often combined chemically with fatty acids to form esters such as the propionate, benzoate, or palmitate. The clinical objective of these procedures is the production of a tissue depot from which steady absorption of an optimal amount of estrogen will occur for periods of several days. Experience indicates that this period between successive doses varies from about 5 to 21 days; it is commonly seven to ten days. Careful description of the subjective results of such therapy by many women makes it certain that the absorption is not as uniform as most clinicians think. In other words women who have learned to recognize the symptoms of the menopause and of the changes in intensity under treatment describe a preliminary exacerbation of discomfort in the first hours after the injection of a large dose in oil. This is followed by the desired relief for a few days and then by gradual return of symptoms. When the latter become severe enough another injection is administered. Such a sequence cannot be called smooth control of a syndrome which lasts for months to years.

Another attempt to provide such smooth control has been made by the implantation of pellets of estrogens in loose subcutaneous spaces. The slow solution of these compounds in aqueous tissue fluids requires several months. Difficulties are that it is harder to establish the adequate dose, an overdose can be removed only by a minor surgical procedure, and local reactions have not been eliminated. These include fibrous tissue encapsulation, limiting absorption in some women, and occasional infection in the pellet or in the process of introduction. This method is not yet to be recommended as a routine procedure.

Since the estrogens are all more easily soluble in oils than in water it has been found possible to apply them in ointment form to the skin, as

on the abdomen, with slow absorption. This has been shown to occur not only in animals (6) but in women (7). These active substances are also soluble in ethyl alcohol. The author has demonstrated in several cases that solutions of estrone or of estradiol in 95 per cent alcohol are absorbed through the skin of the abdomen in sufficient amounts to relieve women from symptoms of the menopause and to cause cornification of vaginal epithelium. These methods are of more theoretical than practical importance. The inclusion of estrogens in cosmetic creams can be expected to have merely systemic effects, which can be produced and controlled with better precision in other routes of administration.

One of the early routes of introducing the estrogens into the body was by incorporating the compounds in hardened gelatin suppositories which were introduced high into the vagina. This method was proved effective (8) but it is seldom economical. It may still be useful in the menopause in those rare situations in which the chief symptom is pruritus in the vagina and vulva. The principal use of these vaginal inserts is for treatment of juvenile gonorrhea.

Finally the obvious route of administration is orally. The estrogens may be given in solid tablet or pill form, in oil solution in gelatin capsules, or in alcoholic elixirs. All of them are physiologically effective when so used but estradiol is so labile that the dose for oral use must probably be ten or more times what is used by injection. In the case of estrone the ratio is more like five times as much orally as parenterally. The disadvantage is slight in use of synthetic estrogens. All such ratios are very rough measures. Likewise it is not yet possible to give as accurate an estimate of the relative doses of the different estrogens in relief of menopausal symptoms as it is in animal bioassay tests. These comparisons could be made only by use of a fairly large group of women whose menopause symptoms followed complete removal of ovarian tissue surgically.

A disadvantage in the use of oily solutions is that these vegetable oils are physiologically foreign substances and are slowly absorbed—or in many cases not absorbed but encapsulated as are other foreign bodies. There has been no extensive study of such oils after intramuscular injection to justify any opinion as to the preferable ones or to indicate the probability of disappearance of the oil from the site of injection. On the other hand animal experiments (9) have confirmed clinical experience of numerous physicians that the oils may remain for long periods, sometimes giving rise to unpleasant symptoms locally. Since oil injection can be replaced by aqueous suspensions of the estrogens, or by oral therapy, it may well be that the use of oil vehicles will disappear from clinical management of the menopause.

Objections to oral therapy have been based on increased cost, due to greater dose, and to disapproval of self-medication. Those who have spoken of the greater cost have usually omitted including in the cost of the parenteral therapy the fees for making the injections. These are a very real factor in total cost to the patient. If the patient is to be allowed to give her own injections then self-medication is in effect. However, this is no more dangerous than in the case of insulin for diabetics. Nor is it any more probable that self-administered injections can be prohibited in one than in the other. The prejudice against patient's injection of insulin broke down when daily therapy became obviously necessary. The important feature of the professional relationship to the patient with menopause symptoms is providing instruction as to dosage, supervision at intervals to be sure the dose is adequate but not excessive, and inquiry to make certain that other aspects of health are being watched. Patients need to report vaginal bleeding, increased leucorrhea, or any unusual symptoms. These precautions certainly do not require that the patient present herself at the physician's office every week or two.

As a positive advantage of oral therapy with any of the estrogens it may be mentioned that many women have found that they can secure distinctly smoother control of symptoms by taking one or more doses daily than by any of the ordinary injection procedures at intervals of a week or more.

DOSAGE

Since the objective was stated as relief of symptoms, dosage may be defined as the

minimum which will accomplish this objective. It is possible to state with the authority of experience that with very rare exceptions it is possible to relieve all the symptoms of the menopause by use of adequate amounts of estrogen. This confirms the belief that the symptoms are due essentially to a decrease in estrogen supply in the woman's body. In making such a statement about complete relief the one caution is that the physician must assure himself that the symptoms in question were not being experienced by the woman long before the menopause. It is apparent that any single symptom of the menopause syndrome may occur from causes other than decreased estrogen production. In terms which a lay woman will understand she may be told that she cannot be rejuvenated but she can be made as comfortable as she was prior to the onset of the menopause, barring intercurrent diseases.

In terms of practical doses the amount required by any woman will be determined only by trial. It is wise to start with generous doses to secure prompt improvement and thereby convince the patient of the value of persisting in the treatment. Benefits may be expected within a week. If relief is not gratifying in this time the dose is to be advanced. If it is complete at once the dose should be reduced. Changes in dose should ordinarily be made at somewhat longer intervals, such as two to four weeks. The objective of complete freedom from typical discomforts is to be kept in mind. If new symptoms are reported, and it is suspected that they may be a part of the syndrome, the dose may be increased for a period of a few weeks' trial.

The contraindications to overdosage will serve also as evidences that too much estrogen is being administered. The commonest is vaginal bleeding after a period of several months of amenorrhea. This should lead to interruption of therapy, with resumption at a lower dosage as soon as flow ceases. The phenomenon of withdrawal bleeding, after sharp reduction in dose of estrogen, may be very confusing here. Bleeding from excessive dose will be observed when there has been no change in amount used for some time but this occurs in only a few women. Such flowing is probably more commonly observed following use of synthetic estrogens than with the steroid or natural hormones.

Other evidences of excessive dosage include annoying leucorrhea, unpleasant stimulation of breast swelling, unwanted increase in libido, or a vague tension state. The identity of any of these as evidences of over-treatment will be determined by reduction of dose with subsequent relief. One should not overlook physical examination of the breasts or bi-manual pelvic examination for flowing or leucorrhea.

As control of symptoms remains complete it is wise to try gradual reduction of the dose from time to time. Sudden withdrawal is more prone to cause bleeding, to lead to sharp return of symptoms, and is therefore not advised. The patient will understand that since the menopause syndrome is evidence of a gradual transition to a period of life without marked activity of the ovaries, she should attempt to reduce her doses gradually. There may occur periods of increased need subsequently and, if so, the dose may easily be raised, or therapy reinstituted if it has been stopped.

A very common tendency of clinicians has been to use two or more estrogens simultaneously or to employ parenteral and oral therapy at the same time. This serves merely to confuse the picture and to render difficult a decision as to really needed doses. There is no genuine advantage to such mixed treatment. It will be simpler to use only one type of preparation in one clinical situation.

EVIDENCES OF PROGRESS UNDER THERAPY

There are three types of data which can be recorded as evidence of success attending use of estrogens in relief of the menopause syndrome. One may inquire about subjective improvement in the list of complaints originally made by the patient. For this purpose it is often wise to have at hand in the written history of each woman a list of those symptoms of which she has complained and to note from time to time which have disappeared or which are of decreased frequency and intensity. From the point of view of the patient this is the most valuable guide to adequacy of therapy. For the vast majority of clinicians it is the only one available.

The study of the gonadotrophic hormone assay in urine (10) has been of importance in arriving at the current concepts of the endocrine changes which accompany and perhaps produce the menopause. As discussed previously, the reduction of the amount of this hormone in the urine is not a necessary accompaniment of clinical success in treatment and hence it is not worth the effort to make this determination for clinical control. In addition, the bioassay technique is a matter of considerable expense and requires a period of a week or more at the least to secure the data necessary for any conclusion as to the physiological changes which have occurred. For clinical control of therapy this method may be disregarded.

Observations on the cytology of the vaginal epithelial cells as obtained by smears is of very much greater significance. The technique for staining and interpretation has been originated by Papanicolaou and Shorr (11) and the most complete presentation of this very helpful method appeared recently from the same laboratory and clinic (12). It is not at all necessary that such stained smears be used in clinical relief of women with menopausal symptoms. Problem cases can be studied in this way, however, and doubts about the presence or absence of significant amounts of estrogenic material can be resolved with objective evidence. The change from an inactive to an active epithelium indicates either production of estrogen by the patient or administration of such substance in effective doses. It must be recalled that clinically effective dosage, *i.e.*, sufficient to relieve symptoms, may be less than enough to achieve complete maturity or cornification of the superficial vaginal epithelium. In other words this objective method of control of therapy is really needed in only those cases where finer diagnostic discrimination is desired or where clinical research is to be conducted.

ANCILLARY THERAPY

Every physician who attempts to treat a woman in the menopause syndrome should be prepared to undertake a species of psychotherapy. This is no more than what any clinician must expect to do for a patient who has mental aspects of a physical disorder. First he should make it evident that he is trying to understand the point of view of the woman whose attitude to herself, the members of the family, and her social situation is undergoing a marked change. Similarly he should help the woman to realize that this is evidence of a transition from a part of life which has been subject to the continuing and vigorous stimulation of ovarian hormones into the succeeding period in which this stimulation is becoming less intense. Mental capacity is not changed, emotional possibilities are not different in quality, but the intensity factor is altered. The outlook is therefore for increased placidity. During the transitional months or years it is important that patient, family, friends, and even the physician exercise patience and self-control. The phenomena are essentially temporary. A woman who is going through this period of readjustment may need to be cautioned about the number of responsibilities she carries but it is usually most unwise to allow her to reduce social contacts too greatly. The tendency to withdraw from others may lead to undue introspection and augment the tendency to a psychosis which is sometimes seen. Treatment of women with estrogens has often averted psychotic tendencies and probably has also interrupted the milder forms of the involution psychoses (13). If progress in relief from the mental symptoms is not evident within a few weeks after relief from the autonomic complaints appears, the services of a specially trained psychiatric consultant are advisable.

In a small proportion of menopausal patients it is considered unwise to use estrogens. This is true whenever there is or has been carcinoma of the breasts or of the pelvic organs. The reasoning is that estrogens provide one of the most potent stimuli to growth of these tissues and hence should be withheld from such women. There is no recorded clinical evidence on this point and fear of using moderate amounts of estrogen in women who have had carcinomas removed is apparently decreasing, if one may judge by the tone of recent commentators (14). Another situation which is held to contraindicate use of estrogens is the oc-

currence of endometriosis, with transplants of endometrium to peritoneal surfaces. Surgical removal of all such transplants is not feasible, hence therapy for such painful endometriosis involves surgical ablation of the ovaries, full doses of x-rays to accomplish inactivation of the ovaries, or sometimes both steps. The administration of estrogen after such a procedure may lead to continued activity of endometrium wherever it occurs. Various opinions are entertained as to how long a time is required after complete inactivation of the ovaries before atrophy of endometrium may be expected to be so complete that estrogenic therapy will not reactivate the endometrium. Evidence on this point is not available. At the worst, use of estrogens would cause recurrence of pain but the therapy could be interrupted if this should occur.

If the clinician decides that estrogens are inadvisable but that symptoms require medication, the alternative is the use of simple sedatives. Use of one of the many barbiturates is perhaps too ready a refuge for the puzzled doctor and patient. Bromides have disadvantages in their tendency to cause rashes or psychoses. For insomnia, use of chloral hydrate or of paraldehyde may be very wise. In these situations frank discussion of the problem with the woman will often make it easier to hold the sedation at a minimum.

There has long been noted a tendency by clinicians to prescribe thyroid for women in the climacteric. Perhaps this was suggested by the emotional depression, perhaps by the frequent but certainly not universal tendency to weight gain. Use of thyroid is usually not only not helpful but adds to the difficulty. Thyroid is stimulating and increases the instability of the autonomic system, which is already overactive. Thyroid may be used in too large doses and contribute to tachycardia and especially to heart consciousness. Treatment of obesity by use of thyroid is one of the most futile ways of relieving weight excess (15). It is urged that thyroid should be used during the menopause, as otherwise, only when there is real indication of hypothyroidism. This is rarely encountered without genuinely low basal metabolism. If there is doubt, an examination of the serum-cholestrol concentration should be made.

SUMMARY

Diagnostic study should precede any therapy, to make sure that the change in menstrual rhythm is truly indicative of the menopause and that no neoplastic contra-indications exist. The objective of treatment is the relief of symptoms, not re-establishment of flowing, nor the reduction in excretion of gonadotrophic hormone or the alteration in vaginal cytology. Materials available include the several natural steroids—estradiol, estrone, and estriol, in several combinations and vehicles, and a few synthetic compounds, of which diethylstilbestrol is best known. The detailed advantages of these items are presented. The routes of administration include injections, implantations, inunction and oral therapy, the last being held preferable. Dosage must be varied to fit the need of the individual, starting high for quick benefit, and being reduced gradually. Contra-indications in the form of overstimulation of breast and genital activity or of neoplastic growth must be watched for. Progress of the patient under therapy is to be gaged by relief from symptoms, not by any changes in pituitary or estrogenic hormone levels determined by bioassays. Along with such a program of treatment it is important that the patient be treated as a person, sometimes requiring simple psychotherapy.

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The Psychological Treatment of the Menopause

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THE ESSENTIAL psychosomatic nature of clinical endocrinology comes out with particular clarity in case of the climacteric disorders. In the older convention the symptoms of the menopause were arrayed in two categories, the physical and the mental. In actuality, however, the two aspects are so intimately intertwined as to render them practically inseparable. Even in case of the most effective specific hormone therapy, it is often an open question to what extent the benefit is determined by so-called psychological reactions rather than by direct corrective influences upon the organic processes. Perhaps it is, on the whole, to the advantage of the patient that the confident administration of an estrogen has potent suggestive value in addition to any physiological influences it may exert. But the physician, at least, should be sophisticated in the matter and thus be in position to set up the most adroit type of case management in any given instance. Often much is to be gained if, in addition to hormone resources, the physician is able systematically and wittingly to bring to bear appropriate psychological measures. The very physician-patient relationship is inevitably an important element in the treatment; even when the physician regards himself as an uncompromising organicist, the feeling of security that his ministrations confer upon patient is often the most potent factor in his therapy.

A comprehensive discussion of the psychology and the psychotherapy of the menopause would go well beyond the scope of this paper. A brief discussion may be offered, however, of a few of the more important issues—enough, perhaps, to indicate the current trends in the psychosomatic approach. The essence of that approach is to regard simultaneously both the psychological and the organic aspects of each case, superimposing the one upon the other.

The central feature in the menopause, from the somatic point of view, is *over-responsivity of the sympathetic nervous system.* It is through this agency that the characteristic hot flashes, as well as various other perturbations at the physiological level are brought about. That such over-responsivity is primarily of organic origin is indicated by the studies of Hoskins and Wheelon (1) in 1914. These investigators showed that extirpation of the ovaries in dogs resulted in marked increase of vasomotor reactivity as shown by the response to injections of nicotine, which is a selective sympathetic stimulant. Subsequent implantation of viable ovarian tissue to a considerable extent restored sympathetic placidity. That the results of these experiments are transferable to the human species is indicated by the old observation (Hannan) that by injections of adrenalin hot flashes can be induced in climacteric women at will.

From the psychosomatic point of view the central feature of the menopause is *anxiety* with its accompanying tension which leads via the hypothalamus to more or less frequent bombardment of the over-sensitive sympathetic system with disturbing nerve impulses. It is to this anxiety that psychotherapy is primarily addressed—just as is drug sedation. The remainder of this discussion will be devoted, therefore, to the causes and alleviation of anxiety.

The most important source of anxiety is the patient's own conception of herself as a human being. All her life—if she has escaped dire

poverty with its ever-recurrent threat to personal survival—she has been most deeply concerned with a single problem, that of maintaining her own sense of self-worth at as comfortable a level as possible. From early childhood on, every individual casts himself in the leading role in his own particular drama of life. A fundamental purpose—if not the most fundamental purpose—of his every day strivings is to win applause for the hero of the play. In this, he functions, however, not only as actor but also as chief spectator. More technically phrased, the chief purpose of human existence, as seen from within, is "ego maximation" or gratification of the "self-regarding instinct." The means to this end are as varied as are the facets of life itself. At one extreme we see the Mark Tappleys who seek to enhance self-estimation by rising above adverse circumstances; on the other, Uriah Heeps who glory in becoming paragons of "'umbleness." "Keeping up with the Joneses" is motivated primarily by the desire to avoid displacement from the spot-light on the personal stage. Illustrations could be multiplied indefinitely. In the case of well-balanced individuals an unassertive attitude of dignity and good demeanor is the usual means to the preservation of self-esteem.

The most potent cause of menopausal anxiety is the threat that it offers to the ego. The threat operates principally at the instinctual level but to some extent also at the level of consciousness. The function of bisexual reproduction, with its often inordinate cost to the individual, must necessarily have been implemented by highly potent drives—by what might be called the erotic imperatives. Both by inherent impulse and by decades of conditioning, reproductive activity—or the capacity for such activity—is a fundamental, symbolic token of personal worth. The parent, in a literal sense, shares the outstanding attribute of the Creator. However little the reproductive capacity is utilized or however firmly one has consciously repudiated the function of parenthood, at the instinctual level sexual capacity is still a token of power. The menopause amounts both literally and in the expanded Freudian sense, then, to castration. It is inevitably followed by at least some degree of "castration anxiety."

At the conscious level the menopause pronounces an unmistakeable verdict of senescence and carries the threat of senility to follow. To biological uselessness is to be added approaching social inutility—or worse, social dependence. It is only by gallant mendacity that the superannuate can muster even a semblance of acceptance of the poet's

> "Come and grow old with me
> The best is yet to be."

That "best," he knows, must connote a "good" that he, as a biologically sound individual, never had accepted and never could have accepted in more potent days. Hence the threat to the ego, with a greater or less degree of anxiety.

In addition to the symbolic meaning of the menopause as "castration," it affects the "self-regarding instinct" in other ways. For example, the fatigability of that epoch is important. This follows from the fact that self-respect is largely promoted by accomplishment. By that token any enforced curtailment of customary constructive activities by so much lessens the individual's feelings of self-worth. Again the ego is threatened and again anxiety mounts. "I guess I'm gettin' old," with whatever assumed jocularity it may be pronounced, expresses an apology for lessening ability.

Another factor that is frequently associated with the menopause, though not actually a part of it, is the curtailment of family responsibilities that occurs at about the same time as the climacteric. The children have grown up and left the home and the opportunities for services to them are largely lost. With this deprivation of "duties" the "rewards" are likewise diminished and all the factors that make for self-disapproval are to that extent given freer range and with further increase of the anxiety.

It is at the menopausal age, too, that the social circle outside the home often begins increasingly to contract. Friends die or depart and it is more and more difficult to replace them. In every-day terms, the rewards of friendship diminish. But a deeper principle is

involved. One of the chief resources for keeping up the sense of self-worth is identification with others whom one respects. The larger that the "we" figures in one's thoughts and feelings, the larger is the "I" component in the "we." Rotary Clubs, fraternities and many other formalized social groupings get their psychobiological warrant from this ancient ancestral mechanism. It is, actually, the mechanism that nature principally uses to derive the survival value from the gregarious pattern of existence. With the loss of each friend the ego diminishes and with each deprivation, the anxiety increases.

Final mention may be made of one cause of anxiety which is so plain that even the most perverse organicist can not overlook it. That is the threat to economic security that ageing represents. A specter at many a hearthside is loss of the job—either that of the woman herself or that of her husband. The prospect of poverty, or even any significant decrease of income at almost any economic level, not only serves as a threat to the ego but as a harbinger of actual deprivation of the needs or comforts of life. The threat to economic security then adds its quota of anxiety. Obviously, loss of one's savings or their depletion by illness or other mishap has the same general significance.

So much then for the chief psychological features in the menopause. The list is by no means complete and the deeper psychodynamics of the situation have been merely hinted at. However, perhaps enough has been indicated to make the point that the time of the climacteric is a time of increasing anxiety and hence a time of increasing strain upon the sympathetic nervous system. This is superimposed upon an organically determined, enhanced sympathetic reactivity. It is to the vicious circle thereby created that rational therapy has to be addressed.

In this discussion it is tacitly assumed that the individual to be treated is a "normal" woman. Frequently an added compliction is a condition of psychoneurosis or psychosis—a condition that may demand special psychiatric competence if not the aid of institutional facilities.

DIAGNOSIS AND TREATMENT

The first requisite to sound treatment in the menopause as in any other condition which demands therapeutic intervention is a correct appraisal of the problem. What, in the given case, are the significant etiological factors and what is the relative importance of each? If a given woman is a person of well integrated personality and poise she may need no treatment at all. Even in a psychologically stable woman, however, the repercussions of ovarian insufficiency may be so troublesome at the organic level as to render the withholding of estrogen a needless cruelty. But such a patient presents only an elementary problem. Indeed, she may even buy her own "stilbestrol" and fairly successfully treat herself on a trial-and-error basis. But it is with the woman in whose case both organic and psychologic factors demand consideration that this discussion is concerned.

The first diagnostic problem in such cases is the degree of actual ovarian deficiency that exists. If laboratory facilities can be brought to bear, a determination of the gonadotrophin output may be the best index. Lacking the resources for such determinations, a skillfully conducted therapeutic test may suffice for practical needs. This test amounts in effect to ascertaining the responsitivity to a potent estrogen and to a placebo, administered in alternating periods. By and large, any amelioration that can be obtained by the use of placebos serves as an indicator of the operation of psychogenic factors.

If the patient gets adequate relief from placebos an immediate problem arises. Shall the physician content himself with the simple psychotherapeutic resource thereby placed in his hands? Or shall he utilize placebos in addition to other types of psychotherapy? The answer will depend largely upon the physician's own sense of ethics or propriety. In any case, however, he should make sure that he is mendacious only to his patient and not to himself also. A self-deceived physician is a self-blinded one and his deception, while it may succeed in one case, is likely to lead him into pitfalls in the next. To whatever extent facile success with placebos leads the physician to withhold other, more constructive forms of

psychotherapy he is doing less than his full duty by the patient.

Assuming that the given patient is to have the benefit of rational psychotherapy, what are the profitable approaches and methods? These will be more or less obvious if the central problem is visualized for what it is, namely that of anxiety. What is causing the anxiety and how can it be lessened? In other words, what is the psychodiagnosis and the psychotherapy?

As to diagnosis, the theoretically ideal goal is a "deep analysis"—a technical psychoanalysis, hypnoanalysis or other means of uncovering the ultimate psychodynamics of the case. Indeed, in some cases, at least among the psychoneurotics, such diagnositic procedures are necessary to complete success but in the "normal" person much simpler means will usually suffice.

Often no more is needed than one to a few hours of patient, sympathetic listening to the patient's own story. About the only significant advantage that the psychiatrist has over the general practitioner in such cases is that the psychiatrist is conditioned to listen skillfully. It is important in such diagnostic interviews to let it be plain to the patient that the physician is strictly objective and that no issues of moral judgment are involved. As physician he is interested not in sin but in symptoms. Any hint of prudery or censoriousness is likely to cause the suppression of valuable information. The patient is likely to have all that she can manage in overcoming her own reticences and impulses to protect others who may be involved in her story without having also to placate a critic. Often no more than sympathetic attention is needed but sometimes reassuring remarks or stimulating questions may be needed either to get the patient started in her recital or to boost her over some of the restraining psychological walls. If questioning is required special care should be exercised, however, to avoid any type of suggestion that would lead to distortion of the story or, particularly, that would bring out evidence in support of the physician's own preconceptions. While it is doubtful that the self-revelation of a simple interview ever actually gets to the bottom of anyone's personal difficulties, sufficient material will ordinarily be uncovered to permit the bringing to bear of enough psychotherapy actually to meet the existing practical need. After all, nearly any patient has at least some resources within herself and only aid, not complete rectification of her personality, is necessary. If the interview—or interviews—yield good working answers to two questions the psychotherapy may begin. These are, how much anxiety does the patient have and from what sources does the anxiety spring?

Actually, the psychotherapy has already begun. The very opportunity to tell her story often in itself "takes a great load off her mind" which is the patient's formulation for "lessening her anxiety." Also, if the physician by his unspoken attitude has obviously refused to be the one to cast the first stone, that, too, affords reassurance—i.e., lessens anxiety. And, finally, and often most important, the interview has promoted a feeling of identification. A lonesome and frustrated "I" entered the office, a more contented "we" emerged. Indeed the story—an authentic one—is told of a famous Philadelphia psychiatrist who wrought a marvelous "cure" in a delinquent boy by a dozen "office interviews" in which neither the the psychiatrist nor the subject ever uttered a single word except from the lad a final gruff, "well—good-bye."

The further procedures in the way of psychotherapy will be determined largely by the knowledge gained regarding the etiologic details. If a clear idea is held as to the sources of the anxiety, the means of alleviating it are often obvious. If a "threatened ego" is the predominant source of the anxiety, anything legitimate that can be done to restore a sense of self-worth will be of direct aid. A tacit proffer of comprehending friendship is one potent resource—and one that modest physicians commonly greatly underestimate. The privilege of pronouncing a "we" that includes a respected leader in the community is in itself reassuring. Often, too, the patient's appraisal of herself is faulty—she may have virtues that she has always taken for granted as negligible but that can be pointed out and emphasized with

ameliorative reassurance of the "threatened ego."

Frequently the anxiety-producing loss of the sense of self-worth is due to a passive acceptance of a life pattern that has increasingly led to deprivations of opportunities for accomplishment that the patient respects. She has actually allowed herself to become less and less worthwhile to anyone else and therefore to herself. In such cases ways should be pointed out in which she can extend her sphere of productive activity. But more, she may need to have instilled into her enough enthuasiasm to overcome a considerable degree of initial apathy. What form the activity takes is largely immaterial except that it must be something that the woman herself respects. It may be tray-painting, gardening, sitting with a neighbor's baby, bridge, bandage-rolling or what-not. This is "occupational therapy" in a real, though not formalized sense. In the use of this and related therapeutic modalities the actual goal, however, should be kept in mind, namely the enhancement of the sense of self-worth and the resulting decrease in anxiety. That principle is often of significant aid both in the selection and in the continuance of activities.

One other approach to the problem of the "threatened ego" is actually to expand and fortify it by the various resources of sociability, i.e., of "identification." Direct the patient into a way of life in which she has increasing use for the pronoun "we" and less for "I." Each friendship that one has enhances the ego just as each loss depletes it. And this therapeutic device will be more effective if it involves giving more than receiving. This paragraph could, of course, be expanded into a book—as indeed it often has been expanded. Identification can be used most skillfully, however, in the psychotherapy of the menopause again if the primary purpose is kept in mind, namely that of decreasing anxiety. It is easily possible so to complicate the life of the patient with new responsibilities and incidental annoyances as to defeat the actual purpose.

The most difficult factor to deal with, psychotherapeutically, is the anxiety that results from actual or threatened poverty with its many deprivations and frustrations. The obvious remedy would be so to modify our economic system as to assure at least a modest degree of security for all. How that could be done without a stultifying loss of motivation for thrift and accomplishment, however, is a possibly insoluble problem. At any rate, it is not a topic appropriate to this discussion. There are methods of meeting, in fact, the problem of the anxiety of indigence but they involve a recasting of the philosophy of life. The best that the psychotherapist can do, here, is to share with the patient such enlightenment as he has been able to gather on how best to meet frustrations and fears. But often profitable use can be made of the "uplift literature," also. Among the best of the books that can be utilized for this purpose is Fosdick's *"On Being a Real Person."* This work is not only inspiring in spirit but is also based on an expert knowledge of modern technical psychobiology—an advantage that is by no means universal in such literature.

To reiterate, the patient is beset at once by an over-sensitive sympathetic nervous system and by a variety of anxiety-producing experiences that subject this system to increased assaults. The goal of psychotherapy is to do whatever skill and sympathy direct to allay the anxiety. Any inner placidity that can be induced will to that extent mollify the overwrought sympathetic system.

The problem has, of course, been treated somewhat diagrammatically in thus emphasizing the sympathetic component. Generally speaking, however, the same methods are indicated in dealing psychotherapeutically with the bodily and mental perturbations, however produced, hence no methodological error is involved in focussing attention on the anxiety-sympathetic complex. It affords a goal that is easily comprehensible and one that can be approached on a common-sense basis by the practitioner who has not had inclination or opportunity to acquire psychiatric competence. It goes without saying, however, that such competence would be an added asset both in making case analyses and in bringing to bear therapeutic versatility. Further technical discussion of the aims and methods of psychiatry

can be found in a current article by Whitehorn (2)—an article that assumes no more than general medical knowledge and that affords in brief compass a readable and comprehensive approach.

SUMMARY

It is pointed out that the symptoms of the menopause arise in large degree directly or indirectly from over-activity of the sympathetic nervous system. This over-activity is due in part to an augmented responsivity of that system due to deprivation of the ovarian hormones. It is due in part also to over-stimulation of the sympathetic system by the anxiety that is commonly experienced at this epoch.

Various of the commoner causes of the anxiety are enumerated and discussed and ways of ameliorating the anxiety are suggested.

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2. WHITEHORN, J. C.: Guide to interviewing and clinical personality study. *Arch. Neurol. & Psychiat.* 52: 197. 1944.

ERRATA

Page 199, in the table the headings of the last two columns should be interchanged so that the first is Albumin *and the second* Globulin.

Page 489, junior author's name should read David S. Davis

Page 515, Brougher, J. C.: Parathyroid extract in pre-eclamptic toxemia. *Only a small proportion of the 1800 patients mentioned had pre-eclamptic toxemia.*

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